D. E. Sakas, B. A. Simpson,
and E. S. Krames (eds.)

Operative Neuromodulation

Volume 1: Functional Neuroprosthetic Surgery

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Operative Neuromodulation

Volume 1:
Functional Neuroprosthetic Surgery.
An Introduction

Edited by
D.E. Sakas, B.A. Simpson, and E.S. Krames

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Preface

Operative Neuromodulation is a rapidly evolving multidisciplinary biomedical and biotechnological field that opens new options and possibilities not only for helping patients but also for understanding the role of the nervous system in modulating all other bodily systems. Many specialties are involved and multidisciplinary collaboration is necessary for the further progress of the field. The International Neuromodulation Society (INS) exists to promote, disseminate, and to be an advocate for the science, education, best practice and accessibility of all aspects of neuromodulation. The INS is directly associated with the International Functional Electrical Stimulation Society (IFESS) which aims to promote the research, application, and understanding of electrical stimulation as it is utilized in the field of medicine. The World Federation of Neurosurgical Societies (WFNS) has realised the potential of the field and recently created a Neuromodulation Committee. Undoubtedly, many other neuromodulation committees will be founded in other specialties and all of them, in close collaboration with the INS, will advance neuromodulation. With this book, we aim to facilitate a world-wide dissemination of authoritative information regarding this scientific and clinical field, and to promote an expansion of current medical practice and research into this area. Furthermore, we wish to contribute towards a constructive integrative relationship between the biomedical and technological fields involved in neuromodulation. It is hoped that this book will have a positive impact in the continuously evolving research and practice of neuromodulation.

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An introduction

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An introduction to operative neuromodulation and functional neuroprosthetics, the new frontiers of clinical neuroscience and biotechnology

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Summary

Operative neuromodulation is the field of altering electrically or chemically the signal transmission in the nervous system by implanted devices in order to excite, inhibit or tune the activities of neurons or neural networks and produce therapeutic effects. It is a rapidly evolving biomedical and high-technology field on the cutting-edge of developments across a wide range of scientific disciplines. The authors review relevant literature on the neuromodulation procedures that are performed in the spinal cord or peripheral nerves in order to treat a considerable number of conditions such as a) chronic pain (craniofacial, somatic, pelvic, limb, or due to failed back surgery), b) spasticity (due to spinal trauma, multiple sclerosis, upper motor neuron disease, dystonia, cerebral palsy, cerebrovascular disease or head trauma), c) respiratory disorders, d) cardiovascular ischemia, e) neuropathic bladder, and f) bowel dysfunction of neural cause. *Functional neuroprosthetics*, a field of operative neuromodulation, encompasses the design, construction and implantation of artificial devices capable of generating electrical stimuli, thereby, replacing the function of damaged parts of the nervous system. The present article also reviews important literature on functional neuroprostheses, functional electrical stimulation (FES), and various emerging applications based on microsystems devices, neural engineering, neuroaugmentation, neurostimulation, and assistive technologies. The authors highlight promising lines of research such as endoneural prostheses for peripheral nerve stimulation, closed-loop systems for responsive neurostimulation or implanted microwires for microstimulation of the spinal cord to enable movements of paralyzed limbs. The above growing scientific fields, in combination with biological regenerative methods, are certainly going to enhance the practice of neuromodulation. The range of neuromodulatory procedures in the spine and peripheral nerves and the dynamics of the biomedical and technological domains which are reviewed in this article indicate that new breakthroughs are likely to improve substantially the quality of life of patients who are severely disabled by neurological disorders.

Keywords: Operative neuromodulation; functional neuroprosthetic surgery; neuroprostheses; chronic pain; spasticity; cardiovascular ischemia; functional electrical stimulation; neuropathic bladder; neuropathic bowel.

Definitions

In biology, neuromodulation can be defined as the process by which chemical substances, neurons or neural networks excite, inhibit or tune adjacent or remote neurons or neural networks in order the latter to deliver responses, which are better adapted to the demands of the environment of an organism and more suitable for ensuring its successful survival. In the biotechnological context, neuromodulation is a field of science, medicine, and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical with the aim to improve the quality of life for humans suffering from neurological disorders. In the clinical context, several definitions have been proposed and the most widely accepted are described below. Neuromodulation can be defined as:

a) the science of how electrical, chemical, and mechanical interventions can modulate or change central and peripheral nervous system functioning,
b) a form of therapy in which neurophysiological signals are initiated or influenced with the intention of achieving therapeutic effects by altering the function and performance of the nervous system, and/or
c) the therapeutic alteration of activity in the central, peripheral or autonomic nervous systems, electrically or pharmacologically, by means of implanted or non-implanted devices.

More recently, it has been proposed that neuromodulation is the reversible use of electrical stimulation or centrally-delivered pharmaceutical agents to manipulate nervous system activity in order to treat specific types of chronic pain, spasticity, epilepsy, ischemia, cardiac, bowel, bladder dysfunction, nervous system injury, and movement, visual, auditory or psychiatric disorders [3].

All the above definitions imply that neuromodulation requires the use of implanted technology or device in the body of a patient to achieve a therapeutic goal. Much of neuromodulation, exclusive of external devices such as transcutaneous neural stimulation (TNS) or transcranial magnetic stimulation (TMS), has an interventional or operational character. In most clinical or therapeutic settings, therefore, it is useful to us to further modify the character of neuromodulation by adding the modifier ''operative,'' distinguishing it from less invasive neuromodulatory techniques such as TMS. We call this therapy, ''*Operative Neuromodulation*.'' We propose that *Operative Neuromodulation* is defined as an interventional field of medicine that alters neuronal signal transmissions by implanted devices, either electrically or chemically, in order to excite, inhibit or tune the activities of neurons or neural networks to produce therapeutic effects. This definition is neither the best possible nor the final one to be formulated. Undoubtedly, in years to come, better definitions will be proposed. The difficulty in defining neuromodulation may, in part, reflect the fact that this is a subject with at least two key areas of complexity. Firstly, neuromodulation is a rapidly evolving multidisciplinary biomedical and technical field and, secondly, the procedures are performed on the nervous system, but affect any organ or system of the human body. Currently, the clinical specialists who are involved in neuromodulation come from anesthesiology, neurosurgery, neurology, neurophysiology, cardiology, and orthopedics, but because of the systemic effects and benefits of this therapy, this relatively new discipline of medicine will, most likely, encompass or influence most medical specialties.

The term neuromodulation refers to the use of technology at the neural interface and is a generic term that, today, should supercede many specific terms used in the past including neuroaugmentation, neurostimulation, neural prosthetics, functional electrical stimulation, assistive technologies, and neural engineering. Because these terms are still within our clinical and scientific lexicon, it is worthwhile to define them here although they will be further discussed and refined within the chapters of this volume. *Neuroaugmentation*, a term often used synonymously with neuromodulation, is the enhancement of the nervous system and its activity by implantable devices that convey either electrical stimulation, delivery of drugs or chemicals, or implantation of cells in order to produce therapeutic effects. *Neurostimulation* is the processes and technologies of applying electrical currents of varying parameters by means of implanted electrodes in order to achieve functional activation or inhibition of specific neuronal groups, pathways or networks. A fascinating review of the history and potential applications of electricity in the nervous system is provided in this volume by *Fodstad* and *Hariz*. *Functional electrical stimulation* (FES) is the selective stimulation of motor fibers in order to produce functional muscle contractions by approaching that fibers closely either transcutaneously (non-invasively), subcutaneously (invasively) or by putting an electrode in close proximity to a Ranvier's node within the nerve. FES is electrical stimulation of a muscle deprived of normal control in order to produce a functionally useful contraction. The electrical stimulation that produces only a sensory response cannot be termed as FES and the electrical stimulation that aims only to reduce pain is also not FES. *Assistive technologies* are items, pieces of equipment, devices or product systems, whether acquired commercially or customised that are used to increase, maintain or improve functional capabilities of individuals with disabilities. Assistive technologies encompass products such as wheelchairs, walkers, ramps, communication boards etc. For a review see chapter by *Sakas* and colleagues. *Neuroprosthetics* is a biotechnological field dedicated to the study, design, construction and implantation of artificial devices that generate electrical stimuli by initiating action potentials in nerve fibers in order to replace the function of damaged parts of the nervous system. *Neural engineering* applies methods and principles of engineering, physical and mathematical science to investigate the nervous system and construct technological devices that interface with it. An alternative definition is that *neural engineering* is the science that aims to interface electronics to brain, spinal cord, and nerves by combining the potentials of microsystems technology and microelectronics with the current understanding of the electrochemical, neuroanatomical and neurophysiological properties and constraints of the nervous system. As we see, neuromodulation, defined as the interface of technology with the nervous system to produce benefit to the patient, encompasses all of the varied specific terms above. Neuromodulation, though diverse and encompassing multiple specialties, is specific to the use of technology in impacting positively on the body. It is the fastest growing field of medicine today.

Sections of current volume

The present compilation of articles in this volume, titled *Operative Neuromodulation*, and subtitled *An*

Introduction to Functional Neuroprosthetic Surgery describes techniques whereby engineered technology is applied to the spinal cord or peripheral nerves, either by contact with non-neural coverings (e.g. dura mater), or directly within the fluid media that surrounds the nervous system (e.g. cerebrospinal fluid) in order to influence nervous system function and produce therapeutic benefit. These techniques are invasive and representative examples include epidural stimulation for pain or intrathecal drug delivery systems for spasticity or pain. In addition, this volume includes a section on Functional Electrical Stimulation (FES) techniques which can be termed as non-invasive Functional Neuroprosthetic Systems because they are applied by transcutaneous contact with the nervous system, rather than being implanted.

Neuromodulation lies at the intersection of biomedical and techonological progress and can function as a broad area for convergence, exchange and cross-fertilization of ideas. The aim of the editors is to present a comprehensive and authoritative review on this field. The authors of this volume have been selected because of their contributions or innovative works performed over the years and presented at major international meetings. The included articles within this volume describe what is known about neuromodulation today and span from the state-of-the-art knowledge base of established neuromodulation procedures used at the spinal cord and/or peripheral nerves for pain and spasticity, bladder and bowel dysfunction, and cardiovascular disease to what is known about forefront and more current applications, utilizing biohybrid materials. The volume concludes with neuroprostheses and relevant emerging applications. The authors were asked to place emphasis on both the understanding of the neuronal networks involved and on practical clinical matters such as criteria and guidelines for selecting suitable patients for neuromodulation, descriptions of interventional or surgical technique, the organization of effective multidisciplinary teams, how to deal with borderline cases, and how to evaluate clinical outcome. Special emphasis has been given to the understanding of why some do well, while others do not. Moreover, each chapter gives suggestions for clinical improvements and discusses the personal views of the authors on new directions and opportunities for the future.

Undeniably, the management of chronic pain has been the greatest success story in the field of neuromodulation and much has been written about this indication. The recognized goals of pain treatment are reduction in the intensity of a patient's pain while improving both physical and emotional functioning of the individual. To meet these goals, pain practitioners should be able to use all of the ''tools of the trade'' or, if unable to use them, to refer the patients to the specialists who know how to appropriately use these tools [1]. Spinal cord stimulation (SCS) has been acknowledged as an appropriate and effective therapy for chronic non-malignant pain. The first section of the Volume is dedicated on neuromodulation for pain and starts with a comparative review of ablative versus modulatory spinal procedures (*Burchiel*). Spinal cord stimulation (SCS) has been acknowledged as a treatment for chronic non-malignant pain. Patient selection criteria, surgical procedure, postoperative complications, and clinical outcome following SCS are described by some of the most experienced practitioners of SCS (*Kumar, Rainov, Kuhta, Lanner*). Surgical considerations for improving implantation technique and minimising hardware-related failures are discussed by *Beems, Jenkins, Vangeneugden,* and *Rainov.* The role of peripheral nerve stimulation (PNS) in the management of intractable migraine and craniofacial painful syndromes is underlined in separate articles by *Slavin, Weiner,* and *Rogers*. Finally, the chronic intrathecal infusion of analgesic drugs either as single therapy or, more interestingly, in combination with SCS in the management of intractable back and leg pain are also presented (*Rainov, Koulousakis, Linderoth*).

Chronic intrathecal baclofen (ITB) administration through an implanted pump has become an established therapy for severe, intractable spasticity of spinal or cerebral origin. Pathophysiological mechanisms, guidelines for selecting appropriate candidates, surgical technique, procedure- and device-related complications, and functional outcome following ITB therapy in adult and pediatric populations are presented in detail by *Dykstra, Ethans, Koulousakis, Rietman, Richard, Sakas,* and *Sgouros*. The clinical interrelationships and the outcome of ITB depending on the underlying pathology such as upper motor neuron syndrome (*Rietman*), multiple sclerosis (*Dario*), dystonia (*Richard*), cerebral palsy (*Sgouros*), cerebrovascular disease (*Francisco*) or injury (*Petropoulou*) are presented in detail in this volume. Intrathecal baclofen's effects on functional capacity of patients such as ambulatory ability, ease of caregiving, and self-dependency are discussed by *Dones* and *Marra*. The potential role of chronic ITB therapy in the management of dystonia, in alleviating chronic pain, and in recovery from persistent vegetative state are also presented (*Richard, Taira*). The significance of special neurophysiological tests in the overall management of

spasticity is highlighted by *Stokic*. The role of neurorehabilitation after the initiation of ITB therapy, the significance of close collaboration between involved disciplines, and the future prospects of the field are discussed in the chapters by *Petropoulou* and *Panourias*.

SCS, as effective therapy for refractory lower limb ischemia, is discussed in the chapters by *Sciacca* and *Clayes*, while SCS for angina pectoris and cerebral ischemia is discussed in separate articles by *Moutaery*, *Sagher*, and *Robaina*, respectively. A compelling argument in favor of early use of electrical stimulation in these conditions would arise if it favorably modified the course of the underlying condition. It is also encouraging that, in the relevant literature, there is some evidence of a possible "limb salvage" effect of SCS in a subgroup of patients with critical limb ischemia and a possible cardioprotective effect of SCS in cardiac ischemia [8].

Other uses for electrical stimulation are discussed in several different chapters. Indications for electrical stimulation such as dysphagia and diaphragm paralysis are discussed by *Taira* and *Tyler* and the future directions of the field are summarized. Neuropathic bladder and associated detrusor dysfunction are disabling conditions that occur commonly following severe spinal cord injury. Some of the most well-known investigators (*Barat, Bauchet, Kutzenberger, Rapidi*) describe their research and clinical experience with neuromodulatory therapies for these urologic disorders and discuss, in detail, the anatomic and physiologic foundations, the selection criteria for the use of neuromodulation, the surgical techniques involved, the complications that may arise, the functional outcomes derived, and the future prospects for the field. The current state and the future directions for the neuromodulatory management of fecal incontinence, a severely disabling condition following SCI, through sacral nerve root stimulation, is discussed by *Ratto* and *Matzel*. The potential role of neuromodulatory interventions in modulating sexual dysfunction is discussed by *Meloy. Kothari* discusses the mechanisms of chronic neuropathic pain of pelvic origin and further discusses the role for peripheral nerve stimulation (PNS) in its management.

Functional electrical stimulation (FES)

Functional Electrical Stimulation (FES) holds considerable promise for improving and enhancing motor capacity in patients suffering from severe limb paresis or paralysis, either secondary to stroke, head injury, or neural trauma from intervertebral disc herniation. In their respective articles, *Kanno, Ring* and *Wang* and colleagues present the neural pathophysiology of this disorder, its epidemiological background, the clinical indications for the use of FES, selection criteria of patients receiving FES, and the methodology of FES, particularly for the restoration of function to a paretic or paralyzed upper limb and shoulder, respectively. Sinkjaer *et al*. outline the mechanisms for the action of FES and its role in improving stance and walking ability in patients suffering from lower limb monoparesis. *Donaldson* and *Newham* present, in detail, FES cycling and discuss its future as a method for strengthening paraplegic muscles and supporting walking capacity in patients. Any surface stimulation system, however, has inherent limiting factors including difficulty in repeatedly locating correct points for stimulation, difficulty in reaching deeper lying nerves, lack of selectivity, variation in skin impedance, necessity for resetting pulse-amplitude because of changes in electrode position, discomfort to the patient, and low efficiency of the energy used for activation of the nerve. To actualize the great potential of FES we need answers and effective solutions to the above problems.

Neuroprostheses and emerging applications

Electronic sophisticated and high technological devices that translate the intention to move paralyzed limbs into actual movement offer a broad area for research in the laboratory and clinic and represent a great hope for severely disabled sufferers. Morita, Keith and Kanno describe, in our estimation, one of the most successful neuroprostheses, so far, for patients with tetraplegia or arm monoplegia, which converts minimal shoulder movements into the basic movements of the contralateral arm and hand. *Stieglitz* describes the development and application of micro-, nano-, and biohybrid systems in neurorehabilitation and analyzes their bioethical and social implications. *Koch* provides an elaborate description of tiny electrodes, microelectronics or connectors which are currently used to interface human nervous system and highlights critical elements that should be improved in their design. The direct brain control of FES systems constitutes a great challenge for neuroscientists; *Rupp* and *Ruddiger* discuss how biomedical microsystems might be implemented with a special emphasis in their application for restoring grasping capacity after severe cervical cord injury.

The last section in this volume includes articles on emerging applications. The role of SCS as an adjunctive

treatment to radio- and chemotherapy of high grade gliomas (*Robaina*) and the efficacy of SCS in enhancing recovery from a persistent vegetative state (*Morita*) are discussed in this section. *Riener* provides us with an overview of existing systems that support deficits in movement of the upper limbs that occur after disabling neurological pathologies; each device is compared to others with respect to technical function, applicability, and clinical outcomes. Finally, the future prospects of biological treatments for pain and of baclofen use in various neurological disorders are discussed by *Rainov* and *Dario*, respectively.

Socioeconomic aspects of neuromodulation

Great strides have been made in the development, application, and commercialisation of neuromodulation, FES, and neural prostheses over the last 20 years. Sensory and motor neuromodulation systems have gained FDA approval and European CE marks and widespread acceptance in clinical practice. It is widely accepted that neuromodulation therapies may substantially reduce costs for less invasive therapies including, but not limited to, medications, cognitive behavioural therapies, and physical therapies. Cost-benefit analyses that prove the efficacy and financial gains to health systems from neuromodulatory procedures are increasingly reported [7]. As an example of cost savings of neuromodulation therapy, intrathecal baclofen has been shown to be cost effective because it improves patient's quality of life and reduces the cost of treatment for complications of severe spasticity and hospitalizations. However, and unfortunately, in spite of these obvious cost savings, there still exists a ''value-for-money'' debate within many payor or medical insurance organizations who are asking whether it is even worthwhile to perform neuromodulation, at all.

In spite of this debate, it is a generally accepted principle that appropriate, neuromodulation therapies should not be used at early stages of illness before trialing more conservative and less costly therapies such as pharmacological, functional restorative or behavioural therapies. However, as we learn more about the clinical and cost effectiveness of neuromodulatory therapies, we can begin to make a good case for offering neuromodulation therapies at earlier stages of treatment for many disease processes. Some, in fact, do argue that it may not be justified to delay neuromodulation therapies for any extended period of time because there do exist substantial risks of physical, psychological and social damage due to either ischemia or neuropathic pain, when that pain exists untreated for long periods of time [8]. The success of any neuromodulation intervention, therefore, depends on practitioners finding optimal therapies that work in terms of timing and means for each patient.

It is important that the number of patients, for whom each neuromodulation therapy is appropriate, is relatively small when compared to the total number of patients suffering from any one disease. The editors and authors of this volume believe that potential candidates for treatment should be referred only to neuromodulation specialists, in established, experienced centers because: a) patients should be carefully screened, evaluated diagnosed and selected for treatment by a multidisciplinary team, b) all the facilities, equipment, and professional personnel required for the proper diagnosis, treatment, training, support, and follow-up of the patient should be available, and c) patients with implantable devices must have appropriate follow-up, receive adequate training in the device use, care and overall support. In addition to the above, the practice of neuromodulation within established centers will provide reliable, meaningful, high-level evidence that is essential not only to improve future case selection but also to persuade commissioners, insurance companies, and others to pay for the treatment. Poor case selection not only wastes resources (including hospital beds, surgical time, etc.) but also subjects the patients to unnecessary surgery with all its attendant risks and disappointments [7]. Undoubtedly, the future practice of neuromodulation will be affected by technological advances made in the field and by changing trends in practice, moving away from external therapeutic systems towards internal therapeutic systems and moving towards out-patient neuromodulation care. Furthermore, it is expected that there will be an increased demand for more cost-effective therapies for the less severely handicaped with less severe afflictions.

In order to help patients, worldwide, we should identify the major challenges that should be overcome and address many important issues such as: conducting studies that will provide high-quality data on outcome, obtaining necessary government approvals for new products or applications, maintaining compliance with FDA or European CE product and manufacturing requirements, minimizing reliance on sole suppliers or key distributors and addressing product liability. All these practitioners who have expertise in the field, must reflect on and need to work on the formation of guidelines for patients, doctors and industry regarding the proper application of neuromodulation therapies. Furthermore,

the obvious ethical questions that arise from too close collaboration of health care professionals with the industry that produce neuromodulation devices must be answered by all of us, industry and the clinic, alike. We need to establish ethical standards of practice that guide clinician relationships with industy in a well-defined framework.

Finally, because patients are being denied the benefit of neuromodulatory procedures because of lack of information or mistaken medical or cost considerations, expert opinion regarding neuromodulation should be widely published and disseminated across the world. The International Neuromodulation Society (INS) exists ''to promote, disseminate, and advocate for the science, education, best practice and accessibility of all aspects of neuromodulation''. Importantly, because the disease that we treat and the science of neuromodulation does not belong to any one ''study group'', the INS is founded as a multidisciplinary society to be inclusive of all scientists, physicians, bioengineers, members of the industry, and other professionals who have a primary interest in the field of neuromodulation [1]. The INS is directly associated with the International Functional Electrical Stimulation Society (IFESS) which aims to promote the research, application, and understanding of electrical stimulation as it is utilized in the field of medicine. In 1999, the INS and IFESS became sister societies. The importance of this field has also recently been reognized by the World Federation of Neurosurgical Societies (WFNS), which decided that a special Committee on Neuromodulation should be formed. This Committee, in collaboration with the INS, has the aim of disseminating appropriate peer reviewed information that promotes expert application of neuromodulation treatments across the world.

Future directions

The field of neuromodulation is diverse and highly technical. Neuromodulation, as we define it by this volume, is not only and merely a devices-based field, but a field that encompasses many diverse disciplines including neurophysiology, neuroanatomy, neural networks, computational analysis, bioengineering, metallurgy, chemistry, electrical engineering, psychology, and applied clinical practice. Operative Neuromodulation, as we defined above, is the science of implantation of these diversely conceived and manufactured devices. It is the cutting-edge of development across a wide range of scientific disciplines. In order to enrich the future of neuromodulation, it is important to make great leaps forward in functionality, acceptance and profitability of neuromodulatory devices and neuroprostheses. Such progress will require the input and support of scientists, industry, government, and education and research organizations.

Undeniably, the great challenge is to gain a better understanding of how neuromodulation exerts its diverse beneficial effects, an issue of mechanisms. Reaching a deeper understanding of the mechanisms operant when using these techniques will depend on progress in biophysics, neural networks and neural transmission research, computational biology, and particularly, computational neuromodulation [5]. Also, the enhancement of our capacity to intervene beneficially on dysfunctional neural systems and help patients depends on progress in many new technological fields including neural engineering microsystems technologies, microelectronics, nanotechnologies, biomimetics etc. Such progress is likely to create new opportunities and new fields of clinical practice and research. With respect to neurosurgery, in particular, Operative Neuromodulation does signify a transition of emphasis from the conventional resection of masses and surgical ablative procedures to a ''new surgery'' of neural re-engineering of deranged function.

Conventional approaches

Neuromodulation as a field will be enhanced by the expansion of our list of indications for therapeutic procedures. One such example is the currently explored role of PNS in chronic neuropathic pain, cluster headache, and trigeminal neuralgia. However, the practice of neuromodulation will not grow if our literature continues to rely on published anecdotal material biased by the self-serving evaluations of implanters and will only improve if we base it on the results and conclusions of large randomized controlled trials with sufficiently long follow-up, after implantation. In these studies, patients who have similarities in clinical profiles and implantation times should be compared by independent observers using consistent, valid and reliable measures. Moreover, there should be multiple assessments of outcomes including, but not limited to, pain, but also physical functioning, medication use, work status, health care use, and the impact of the technology on the quality of life of patients. In addition, the neuromodulation practice may improve by the use of computer modelling to predict successful response to neurostimulation and to cus-

tomize the electrodes' position and programming parameters for each individual patient.

Neurotechnological developments

There are many areas where important developments may take place in the years to come. Functional restoration may well involve combined application of what have been considered separate approaches and include:

- *Endoneural prostheses* for peripheral nerve stimulation (PNS); this important line of research has shown that motor fibers stimulation can be more effective if the electrode is placed in close proximity to the node of Ranvier.
- *Closed loop systems* for neuromodulation; these systems represent an important development and aim to be capable of ''responsive neurostimulation'' that is not applied on fixed schedules, but is triggered by central nervous system activity.
- *Hybrid neural interfaces*; these devices are a very exciting area of development and are constructed with the aim to establish connections for communication with regenerating neurons.
- *Spinal cord interfaces*; developments in this area represent a great promise for many unfortunate human beings who have suffered serious spinal cord damage.
- *Intraspinal microstimulation via implanted microwires*; this most exciting work concerns the utility of such products to enable functional movements of limbs in experimental animals after spinal cord injury. It is encouraging that coordinated intraspinal microstimulation of motor neuron cell bodies in the ventral horn produced fatigue-resistant stepping movements [4].

One of the most exciting approaches in rehabilitation of locomotion after spinal cord injury may involve a hybrid neural prosthesis consisting of a mechanical gait orthosis (assistive technology) and electrical muscle stimulation components which power, in part, the orthosis. These may develop to fully implantable systems [9]. This approach may come to a higher level of development if we manage to compensate not only for the motor but also for the sensory deficit in spinal cord injury patients with the application of closed-loop systems, extracting information from either natural sensors (cutaneous, muscular or joint) or from cutaneous mechanoreceptors in order to control, with the use of a ''neural controller'' network, FES-based neural prostheses [2]. Undoubtedly, the limitations of existing neuroprostheses should challenge us to identify new directions for continued research and development towards more complex and intelligent systems. Consumer opinions and frustrations regarding the features and functions of current neuroprostheses should be taken seriously into account in order to design better systems. To satisfy such demands, future developments should aim towards miniaturization and extreme integration of information-technology and information exchange between the neuromodulation system and the patient's body and development of modular systems that can be adapted, altered and adjusted to the patient's specific needs with relative ease.

Neuroprotective stimulation and integration with biological therapies

A close collaboration between all involved disciplines and patients who need and use these devices is of great importance for the development of new neuromodulation therapies. Immense therapeutic potential may arise from the convergence of efforts and close collaboration of patients, biomedical scientists, biotechnological engineers and manufacturers. An area that has not attracted sufficient interest and deserves to be investigated, in the years to come, is the neuroprotective effects of neural stimulation. This is a field of great promise because, in the future, electrical stimulation will be based on advances in neural engineering such as micro-electrode arrays [6] and will certainly be much more refined, precise and therapeutically effective. The potential of all available modalities should be exploited. Particularly, we must answer how electrical stimulation and biological mechanisms of neural repair could work together in order to maximize the recovery of function after CNS damage. One can envisage the use of electrical stimulation not only to alter signalling but to fill neural transmission gaps, to direct growth of axons, and to exert protective effects. Hence, the great new challenge will be the convergence of neural prosthetics with neural regeneration for restoration of function taking into account the current limits of stimulation technology. The most powerful treatment strategies will be those that combine technical innovations, biological approaches and regenerative therapies that work together, interact and amplify the efficacy of each other.

Epilogue

Practitioners and researchers in neuromodulation should have a forward-looking perspective and envision a new era of breakthroughs in the field. There are, how-

ever, certain major issues that need to receive our full attention in order to see further progress. Firstly, as previously stated, it is important to develop guidelines and a better classification of the groups of patients who should receive neuromodulation. Secondly, we must utilize to its full extent the capability of new imaging techniques. Thirdly, it is important to develop the right multidisciplinary teams. Fourthly, we should conduct high-quality studies on both clinical and cost effectiveness. Fifthly, we should strive to integrate advances in stimulation technology with human neurobiology, neuroplasticity, and neural repair and translate problems originating in the medical setting into technological formulations of the problem; by this process, we will make important recent technological knowledge applicable in the clinical environment. The future of neuromodulation, however, concerns more than simply a prediction of exciting technological developments. What actually happens will be the result of a complex interaction between: a shift in mindset away from a dependence upon pharmacological treatment, better awareness and understanding of existing indications and applications, introduction of new indications, better understanding of mechanisms of action, improved case selection, more mature assessment of outcome and better evidence regarding efficacy [7]. In this book, we aimed to achieve three objectives. Our first aim was to contribute towards a constructive integrative relationship between the biomedical and technological fields involved in neuromodulation. Secondly, we wanted to facilitate a world-wide dissemination of authoritative information regarding this scientific field, and thirdly, we aimed to promote an expansion of current medical practice and research into this area. It is hoped that this book will have a positive impact in the continuously evolving practice of neuromodulation. The reader will be the judge of our success in meeting these goals.

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Electricity in the treatment of nervous system disease

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Summary

Electricity has been used in medicine for almost two millenniums beginning with electrical chocks from the torpedo fish and ending with the implantation of neuromodulators and neuroprostheses. These implantable stimulators aim to improve functional independence and quality of life in various groups of disabled people. New indications for neuromodulation are still evolving and the field is rapidly advancing. Thanks to modern science and computer technology, electrotherapy has reached a degree of sophistication where it can be applied relatively safely and effectively in a variety of nervous system diseases, including pain, movement disorders, epilepsy, Tourette syndrome, psychiatric disease, addiction, coma, urinary incontinence, impotence, infertility, respiratory paralysis, tinnitus and blindness.

Keywords: Deep brain stimulation; electricity; electrotherapy; nervous system; neuromodulation; neuropacemaker; neuroprosthesis; neurostimulation; stereotaxy.

"Is it a fact – or have I dreamt it – that by means of electricity, the world of matter has become a great nerve, vibrating thousands of miles in a breathless point of time? *Rather, the round globe is a vast head, a brain, instinct with intelligence; or shall we say it is itself a thought, nothing but thought, and no longer the substance which we dreamed it."*

Nathaniel Hawthorne (1804–1864)

Historical background

By definition, electricity is a fundamental entity of nature consisting of negative and positive charges, observable in the attractions and repulsions of bodies electrified by friction and natural phenomena, and usually utilized in the form of electric currents.

The first known use of electricity in medicine was in AD 46 when Scribonius Largus, a pharmacist from Neron and physician to the Roman Emperor Claudius applied electrical currents from the torpedo fish to treat headaches and painful gout [61, 94]:

"A chronic and intolerable headache which insistently manifests itself can be eliminated at once if treated by applying a live torpedo fish, black in color, to the site of the pain and leaving it there until the pain stops and the part is swollen."

The real breakthrough for electrotherapy came with the scientific progress of the 18th century, especially after the discovery of the Leyden jar in 1746 [11]. In 1777, Cavallo published *"A complete treatise on electricity, in theory and practice, with original experiments."* He reported cures of epilepsy, paralysis, chorea, deafness, blindness, rheumatism and glandular enlargement. He was also the first to recommend electricity as means of artificial respiration [11]. As early as 1774, Benjamin Franklin noted muscle contractions on exposure to static electricity [43]. After Franklin's invention of lightning rods in 1775, there were three important milestones in the history of electrotherapy: The discovery of animal electricity by Luigi Galvani in 1787, the discovery of bimetallic electricity by Alessandro Volta in 1794 and the discovery of inductive electricity by Michael Faraday in 1831 [34, 81] (Table 1). Volta also invented the first electric battery in 1800. In 1804 Aldini, a nephew of Galvani, recommended galvanism for deafness, insanity, amaurosis, and to produce artificial respiration [11].

Andrew Ure in 1818 used the body of a hanged criminal immediately after execution to stimulate the phrenic nerves in the chest with galvanic electricity, thereby producing contractions of the diaphragm [106]. He thought

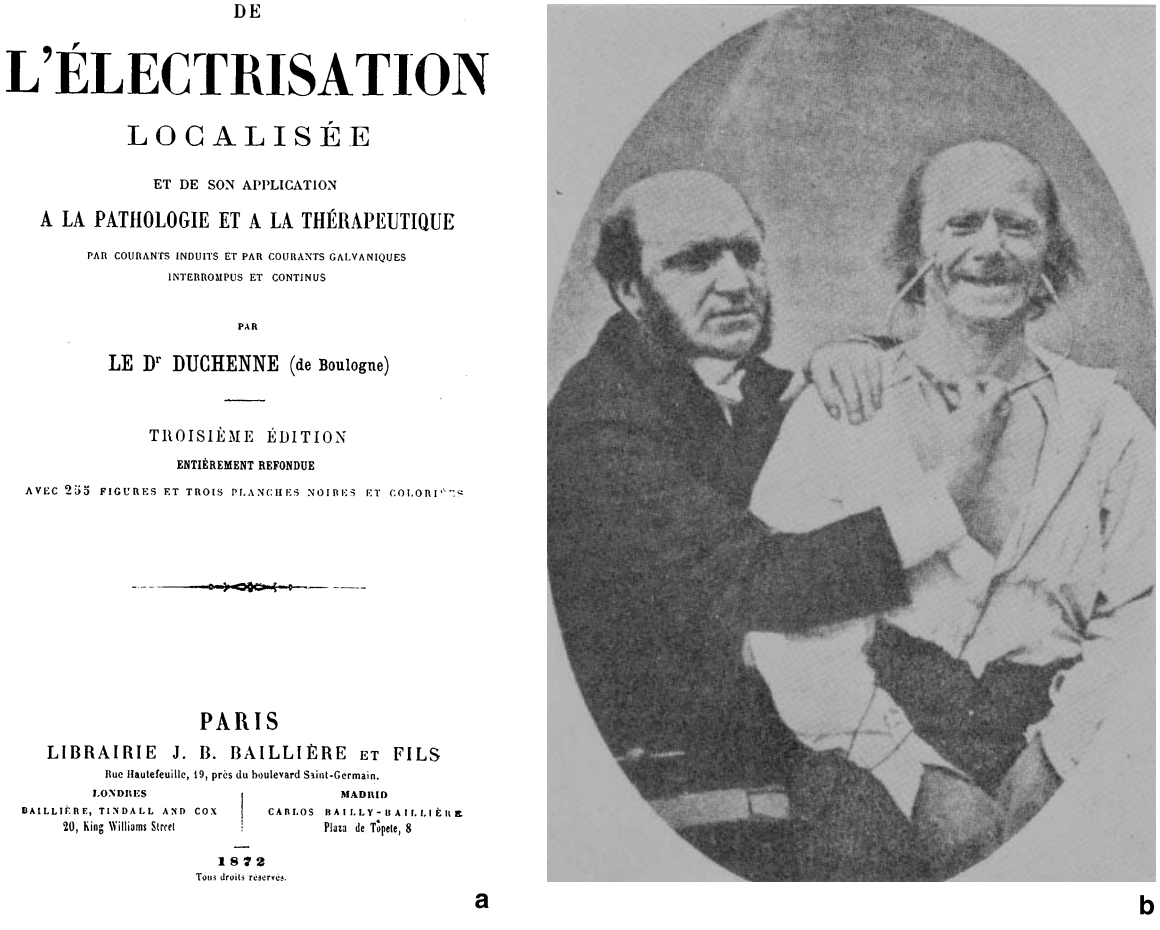
Table 1. *The evolution of electrotherapy*

Torpedo-Fish	
– Scribonius Largus AD 46	
Magnetism and Static Electricity	
– Gilbert	1600
– Leyden Jar	1746
– Wesley	1759
– Franklin	1775
– Cavallo	1777
Bimetallic Electricity	
– Volta	1794
Galvanization	
– Galvani	1787
– Aldini	1804
– Remak	1855
Faradization	
– Faraday	1831
– Duchenne	1855
Electropuncture	
– Salandiere	1825
– D'Etiolles	1840

the method might be used to resuscitate humans with intact vital organs. Ure vividly described the events to the Glasgow Literary Society:

"The left phrenic nerve was now laid bare at the outer edge of the sterno-thyreoideus muscle, from three to four inches above the clavicle; the cutaneous incision having been made by the side of the sterno-cleido-mastoideus. Since this nerve is distributed to the diaphragm, and since it communicates with the heart through the eight pair, it was expected, by transmitting the galvanic power along it, that the respiratory process would be renewed.

The success was truly wonderful. Full, nay, laborious breathing instantly commenced. The chest heaved and fell; the belly was protruded, and again collapsed, with the relaxing and retiring diaphragm. This process was continued, without interruption, as long as I continued the electric discharges. Extraordinary grimaces were exhibited every time electric discharges were made on the


DE

L'ÉLECTRISATION

LOCALISÉE

ET DE SON APPLICATION

A LA PATHOLOGIE ET A LA THÉRAPEUTIQUE

PAR COURANTS INDUITS ET PAR COURANTS GALVANIQUES
INTERROMPUS ET CONTINUS

PAR

LE Dr DUCHENNE (de Boulogne)

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a

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Fig. 1. (a) Title page of Duchenne de Boulogne's monography 3rd edn 1872. (b) Duchenne stimulating the facial muscles in a patient

supraorbital nerve. His countenance was simultaneously thrown into fearful action; rage, horror, despair, anguish, and ghastly smiles, united their hideous expression in the murderer's face, surpassing far the wildest representations of a Fuseli or a Kean. At this period several of the spectators were forced to leave the apartment from terror or sickness, and one gentleman fainted."

In 1824, Flourens in Paris reported on faradic stimulation and ablation of the cortex in experimental animals [72]. The following year Salandiere proposed the use of acupuncture needles in galvanization, so that the current could be applied directly on the desired nerve or organ. The method was called electropuncture and was used for resuscitation by Leroy-D'Etiolles in 1840 [64].

In 1855, the French physician Guillaume Duchenne de Boulogne published his pioneering monography: "*De l'electrisation localisee et de son application a la physiologie, a la pathologie et a la therapeutique"* [31] (Fig. 1a and b). Duchenne was the first to successfully use transcutaneous faradic stimulation of the phrenic nerves for artificial respiration. He was followed by Hugo von Ziemssen, who applied a DuBois-Reymond faradic stimulator (shocking coil) to the phrenic nerve to resuscitate a gas-poisoned patient [34]. At the same time Remak founded a German school of electrotherapy using galvanic current [11]. Interestingly, Duchenne was unwilling to admit the reality of the discoveries of Remak, and Remak rejected the conclusions of Duchenne. A comprehensive overview of contemporary electrotherapie was published by Erdmann in 1858 [32].

Evolution of neurostimulation and lesioning

In 1870, Fritsch and Hitzig [41] observed limb movement when stimulating the motor cortex of the dog, and in 1873 Dittmar used guided electrodes experimentally for the study of the vasomotor center in the medulla oblongata [29]. The first documented account of applying electrical stimulation to the living human brain was in 1874 by Roberts Bartholow in Cincinnati [10]. The patient was a 30 year old woman with an "epithelioma" (meningioma) and an open ulcer in the posterior portion of the skull. Bartholow was able to stimulate the parietal cortex with a "Galvano-Faradic Company double cell battery" and insulated needles. He noted muscle contractions on electrical stimulation which also triggered a grand mal seizure. In 1884, Victor Horsley applied electrical stimulation of occipital tissue in a patient with an encephalocele [109]. The conjugate eye movements he observed led him to identify the stimulated tissue as lamina quadrigemina. Ewald's investigations in Germany in 1896 may have been the first where the brains of fully awake, unrestrained animals were stimulated over a long period of time [107]. Talbert described the technique and his own extension of Ewald's work in 1900 [100].

In 1908, Victor Horsley and Robert Henry Clarke applied their stereotactic instrument and electricity to study cerebellar structures and functions in monkeys [57]. They described in detail the use of direct current (versus radiofrequency) to make lesions, a technique later adopted in animal experiments worldwide [38, 78, 84]. In 1912, Clarke wrote about his instrument [38]:

"This invention relates to what may be termed stereotaxic surgical apparatus for use in performing operations within the cranium of living human beings."

Clarke's prophecy became reality 35 years later when Spiegel and Wycis performed the first stereotactic operation in man [96, 97]. In subsequent years, electrical stimulation and recordings from selected subcortical regions through stereotactically implanted probes were performed in patients with parkinsonism, epilepsy and psychiatric disease by Magnus Petersen [107], Robert Heath [53–55], Carl Wilhelm Sem-Jacobsen [88–91], Orlando Andy [5], N P Bechtereva [12] and Jose Delgado [27]. Alberts and coworkers documented the improvement of dystonia with intracerebral stimulation in awake patients [2, 3].

Sem-Jacobsen was a controversial Norwegian psychiatrist and neurophysiologist. In 1963, he published an article about depth-electrographic observations in psychotic patients [88]. He stated that *"electrical stimulation in some regions in the ventro-medial part of the frontal lobe resulted in a temporary improvement to complete freedom from symptoms"*

Sem-Jacobsen was accused by Norwegian colleagues of receiving grants from the CIA to perform experiments on mentally ill patients. His name was cleared by a government appointed review commission in December 2003, twelve years after his death.

Jose Delgado used remote radio stimulation of bulls' brains to abruptly stop their aggressive behavior in the arena [107]. In 1965 he summarized [26]:

"Autonomic and somatic functions, individual and social behavior, emotional and mental reactions may be evoked, maintained, modified, or inhibited, both in animals and man, by electrical stimulation of specific

cerebral structures. Physical control of many brain functions is a demonstrated fact, but the possibilities and limits of this control are still little known".

In the nineteen twenties, Walter Rudolph Hess in Switzerland and Stephen Ranson in USA used electrostimulation to explore the different regions of the hypothalamus and related neural structures in animals [56, 83]. Their experiments provided support for the speculative theory proposed in 1937 by James Papez that the limbic system (cingulate-hippocampus-fornix mamillary bodies-anterior thalamus) in conjunction with the hypothalamus may constitute the anatomical circuit which regulates emotions [79] (Fig. 2a and b). In 1948, Hess postulated that the hypothalamus consists of an anterior *trophotropic zone,* which dominates during resting and restorative activities, and a middle-posterior *ergotropic zone,* which regulates physiological reactions accompanying high arousal levels [56]. Hess received the Nobel

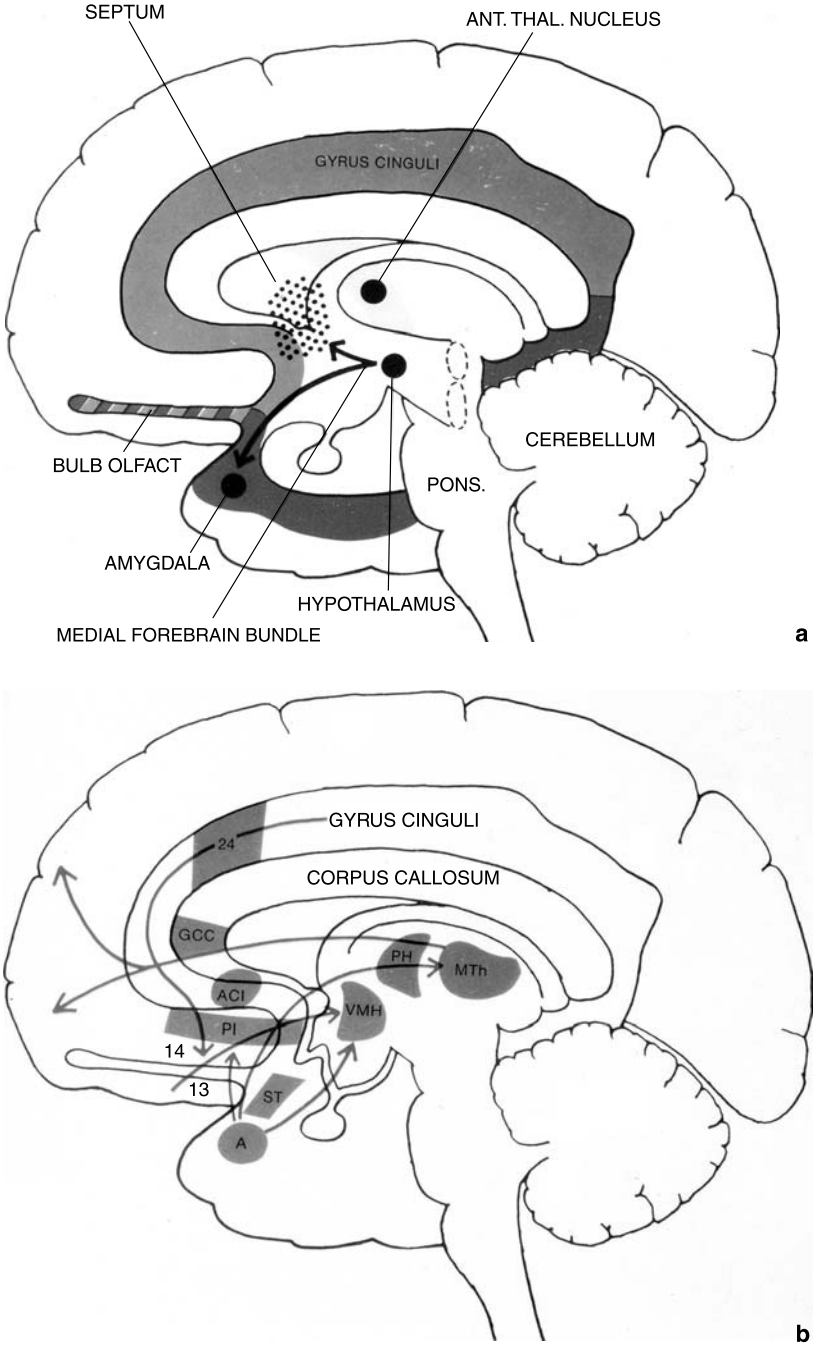

Fig. 2(a). The limbic circuit. (b) Subcortical targets in psychosurgery

Prize in Physiology and Medicine 1949 for discovering the role played by certain parts of the brain in determining and coordinating the function of internal organs. He shared the prize with the Portuguese neurologist and politician, Antonio Egas Moniz, who introduced prefrontal lobotomy for psychiatric disease [33]. This highly controversial procedure was soon to be replaced by less destructive psychosurgeries using the stereotactic technique [33, 36, 63, 75]. Concurrently, electroshock therapy for psychiatric disease and depression was introduced by Ugo Cerletti [20]. Based upon Hess' studies Sano in 1970 described the effect of electrical stimulation of the posterior hypothalamus in man [87]. Stereotactic thermolesions in the *ergotropic triangle* in 51 patients with pathologically aggressive behavior produced marked calming effect in 95% of the cases. The procedure, which was called "sedative therapy" encouraged a German group to perform stereotactic hypothalamotomies in 20 cases of pedophilia, hypersexuality and exhibitionism "*with complete harmonization of sexual and social behaviour"* [73]. A few years later, Nadvornik and his group in Bratislava published a paper on thermolesions in the anterior hypothalamus for "hedonia," which they defined as *"not only excessive smoking, tobaccoism, but also excessive inclinations to good eating and drinking, lucullianism and bacchism"* [74].

In 1974 Quaade, Vaernet and Larsson performed stereotactic stimulation and electrocoagulation of the lateral hypothalamus in obese humans [82]. Three patients with gross obesity subjected to lesions in the lateral hypothalamus showed *"a statistically significant, but transient decrease from preoperative to postoperative spontaneous calorie intake."*

Despite the reported effectiveness of hypothalamotomy as a method to control behavioral disturbances, serious moral, ethical and legal objections to these procedures have been raised [33, 65, 107].

As stereotactic neurosurgery progressed, stimulation became routine for localization of targets in the brain. Hassler, a former graduate researcher with Rudolph Hess, recognized that thalamic stimulation caused cessation of tremor and might mimic the same effect as a lesion [51, 52]. Similar observations of the stimulation of various subcortical targets were made by Spiegel and colleagues [43, 98] and Ronald Tasker and his group [101].

Melzack and Wall's "gate control theory of pain" published in 1965 [69] laid the foundation for the start of pain management by neuromodulation, including transcutaneous electrical stimulation (TENS) [62], peripheral nerve stimulation [99, 111], spinal cord stimulation [76, 92], cortical stimulation [60, 105], and deep brain stimulation (DBS) [58, 70, 85]. DBS and spinal cord stimulation were also used for treatment of spasticity and dyskinesia [93, 95]. Early neurostimulators consisted of extracorporeal parts (radiotransmitter and antenna) and implanted components (receiver and electrode) [42].

Electrophrenic stimulation (diaphragm pacing) for chronic ventilatory insufficiency was developed by William Glenn in the 1960's [45, 46]. The initially enthusiastic reports on spinal cord stimulation in multiple sclerosis could not be substantiated in later trials [21, 43]. Visual cortex stimulation for blindness was first described by Brindley in 1968 [18], and the first clinical study on the use of vagal nerve stimulation for intractable epilepsy appeared in 1990 [47].

Current use of neuromodulation

Neuromodulation is defined as the use of electrical stimulation by implanted stimulators to treat various neurological conditions [1, 43]. Neurostimulation has experienced a renaissance in the past two decades with the introduction of totally implantable neuropacemakers and image guided surgical systems, and the field is rapidly advancing [66]. Neuroaugmentation to subcortical structures via implanted electrodes has largely replaced lesioning all over the world. DBS is a nonablative and reversible procedure with a low incidence of permanent complications, and it is considered safer than ablative lesions. The anatomical targets in the brain for DBS remain more or less the same as for stereotactic radiofrequency lesioning.

The current FDA (Food and Drug Administration) approved indications for DBS in the United States are unilateral or bilateral stimulation of the ventralis intermedius (Vim) nucleus of the thalamus for essential tremor and parkinsonian tremor, and unilateral or bilateral stimulation of the internal globus pallidus (GPi) and subthalamic nucleus (STN) in Parkinson's disease [13, 14, 71]. FDA approval was based on the report of 'The Deep-Brain Stimulation for Parkinson's Disease Study Group' published in 2001 [103]. However, the report has been subjected to criticism for inaccurate documentation of side effects [49]. Benabid introduced STN as the main target in Parkinson's disease, but STN stimulation is hampered by psychiatric side effects due to the nucleus' proximity to hypothalamus and the limbic circuitry [14, 80].

Some DBS surgery complications may be closely related to the experience and techniques of the neurosurgical team. Hardware complications (electrode migration, lead breakage, stimulator malfunction) and other side effects occur in a significant number of patients [16, 42, 50, 77]. The use of single-cell microelectrode recordings for alleged accurate target placement of the electrode, which has become routine in many centers, may increase the surgical complications, including hemorrhage [48]. The modern neuropacemakers require repeat programming of the electrical paradigms by a specially trained health employee to meet the changing needs of each individual patient. The implanted non-rechargeable batteries need to be changed every three to five years.

The exact mechanism of action of DBS is not yet known. Possible mechanisms include depolarization blockade, channel blocking, synaptic failure, antero- and retrograde effects, effects on non-neuronal cells, effects on the local concentrations of ions or neuroactive molecules, and neuronal energy depletion [68]. The long-term effect of chronic electrical stimulation on brain tissue and function is not well understood.

The indications for DBS in movement disorders include (but are not limited to) tremor, bradykinesia, dyskinesias, rigidity, dystonia and gait disturbance [7, 17, 24]. In addition, DBS has been reported to be successful in treating chronic deafferentation pain [58], cluster headaches [9, 39], epilepsy [15, 22, 108], obsessive-compulsive disorder [4, 6], Tourette syndrome [110], depression [59, 67], violent behavior [40] and other neuropsychiatric disorders [86]. Motor cortex stimulation has been applied for chronic pain [60, 105] and the auditory cortex has been stimulated magnetically and electrically for intractable tinnitus [25]. Transcranial non-invasive magnetic stimulation has been reported by several authors to be effective in controlling intractable epilepsy [28, 102]. Neurostimulation and neuromodulation is also used for restoration of hand function and gait [1], improvement of peripheral circulation [8, 30], bladder control [76], fertility management [1], respiratory paralysis [37, 46], chronic hiccup [35], blindness [44], cerebral palsy [23] and coma [104].

DBS is now an established method in treating movement disorders and pain. Thanks to functional imaging, new areas in the brain are shown to be involved in some pathological processes. These areas are now being subject to DBS to see if they can be electrically inhibited [9, 66]. DBS should still be regarded as experimental in psychiatric disease and embryonic in many other mentioned disorders until the reported results have been verified in controlled studies in a larger number of patients. DBS should be considered only for patients in whom other established therapeutic modalities have been carried out. Current practice and ongoing trials of DBS including brain targets are shown in Table 2a and b.

History seems to repeat itself, as electricity is currently being tried for almost any kind of nervous system disease with physicians looking for specific stimulation targets in the brain for certain symptoms and diseases. Neuronal circuits rather than specific nuclei are frequently targeted, and different targets often respond equally to electrostimulation for the same disorder. The voluminous recent literature on DBS indicates that it is in danger of becoming a new method in search for more diseases.

Table 2. *(a) Routine use of dbs*

Parkinson's disease
– Nucleus ventralis intemedius (Vim), globus pallidus internus (GPi), subthalamic nucleus (STN), zona incerta
Dystonia
– Globus pallidus internus (GPi)
Tremor (essential, cerebellar and MS)
– Nucleus ventralis intermedius (Vim), zona incerta
Choreoathetosis
– Nucleus ventralis intermedius (Vim), nucleus ventro-oralis posterior (Vop), globus pallidus internus (GPi), zona incerta
Deafferentation pain
– Nucleus ventro-postero-medialis (VPM), nucleus ventro-postero-lateralis (VPL), Centromedian nucleus (CM), periaqueductal gray (PAG), periventricular gray (PVG)

Table 2. *(b) Current trials of dbs*

Epilepsy
Anterior thalamus, centromedian nucleus (CM), subthalamic nucleus (STN), hippocampus
Cluster headaches
– Posteromedial hypothalamus
Obsessive compulsive disease
Anterior limb of the internal capsule, nucleus accumbens
Tourette syndrome
– Centromedian nucleus (CM), nucleus ventro-oralis internus (Voi), globus pallidus internus (GPi), periventricular gray (PVG)
Depression
– Anterior limb of the internal capsule, nucleus accumbens, anterior cingulum
Drug addiction
– Nucleus accumbens
Violent behavior
– Posteromedial hypothalamus
Obesity
– Anterior hypothalamus

The only commercially available deep brain stimulator (Medtronic Inc) is unreasonably expensive, and aggressive marketing and sponsoring by the sole supplier raises concerns about conflicts of interest.

Thanks to past trials and errors together with scientific progress and technological advancements, we have reached a point where electricity can be applied relatively safely and effectively in the management of a great variety of nervous system diseases. However, improvements in screening and standardization of techniques will be needed in the future. There remains no consensus on best DBS practices, and the refinement of transplantation procedures and controllable genetically engineered stem cells may render these systems irrelevant and obsolete in the future. In the world of contemporary neuroaugmentative procedures, one must always keep in mind the cautionary words of Malcolm Carpenter, renowned neuroanatomist [19]:

"Personally, I feel that stereotaxic surgery has much to offer, if properly controlled and used judiciously. Some of the wild things that are done without a scientific rational jeopardize the entire effort."

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The current range of neuromodulatory devices and related technologies

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Summary

The pace of technology dictates changes in every aspect of human life. Medical profession is not an exception. The development of sophisticated electronic devices has radically influenced diagnosis and therapy. Today neurosurgical science is revolutionized with numerous implanted and non-implanted devices that modulate and stimulate the nervous system. Physicians, patients and non-technical experts involved in this field need to understand the core mechanisms and the main differences of this technology so that they can use it effectively. It will take years until clinicians reach a ''consensus'' about the use of these devices, but in the course of action objective information about the current status of the methods and equipment, and the technical, biological, and financial complications that arise in practice will speed up their public approval and acceptance.

Keywords: Neuromodulation; neurotechnology; neurostimulation; neurodevices; neuroprostheses; brain-computer interface (BCI); assistive technology (AT); functional electrical stimulation (FES).

From neurotechnology to neuromodulation

According to the International Neuromodulation Society, ''*Neuromodulation is defined as the therapeutic alteration of activity in the central, peripheral or autonomic nervous systems, electrically or pharmacologically, by means of implanted devices*'' [13]. In this usage, neuromodulation is another form of technology where the knowledge about the nervous system is used to create specially designed implantable devices to serve a therapeutic or rehabilitation purpose. On the other hand our current efforts combine technical methods, skills, processes, equipment, and information from biology (biochips, genetic engineering, and cellular implantation), neuroscience, mechanics, electronics, computing, and pharmacology in order to surpass the field of neuromodulation. This interdisciplinary nature of the fields combined is reflected in the term ''neurotechnology'', a multi-billion dollars industry that includes three sectors [17]:

1. Neurodiagnostics (neuroimaging, in vitro diagnostics, neuroinformatics).
2. Neuropharmaceutical (cogniceutical, emoticeutical, sensoceutical).
3. Neurodevices (neurostimulation, neuroprosthetics, neurosurgical).

More specifically, recent advances in the fields of neuroscience, robotics, and electronics have caused a resurgence to develop neurodevices for interaction with the impaired neuro-muscular and sensory system in order to restore or decrease the impact of a disease or injury on the individual. For example, in an attempt to bypass pathological motor or sensory nerve circuits, implantable or non-implantable devices have been invented to restore vision, hearing, motor, and sensory function.

In this review, we classify and summarize the current state of neuromodulation related technologies i.e. neurostimulation and neuroprosthetics. The third category, neurosurgical devices for navigation, radiosurgery, and endovascular intervention is beyond the scope of our review. Apart from the classification criteria in the next sections we define terms related to the technology used for the development of neurodevices and we present a short description for each type of device, an abridgment of the surgical operation required and an application example. In addition, we give a short description of the similarities of Assistive Technology (e.g. wheel chairs, artificial limbs, augmentative-alternative communication) with the neurodevices and we conclude our review with frequently met issues i.e. complications and risks, financial implications, and future prospects.

Classifications of neurodevices

Rehabilitation is an application field for implantable neural devices. Diseases and traumatic incidents may lead to damage or lesions in the central or peripheral nervous system. When the information flow between any of the following: brain, spinal cord, nerves, biological sensors and actuators, or muscles, is interrupted, sensoric inputs are lacking and vision or hearing is lost. If motor commands from the brain do not reach the muscles, paralysis occurs. The objective of neural rehabilitation is the restoration of lost functions using therapeutic programmes and technical aids. Because of the tremendous complexity of the human nervous system, technical aids only lead to restricted restoration in function. However, what may seem to be a small improvement to a healthy person may be a great improvement in quality of life for a disabled person.

Neurodevices can be classified according to the following criteria:

- stimulation (i.e. pharmacological vs. electrical);
- application (i.e. neuroprosthesis vs. neuro-orthosis);
- purpose (i.e. therapeutic vs. assistive vs. rehabilitation);
- site (i.e. implantable vs. external);
- invasiveness (i.e. invasive vs. non-invasive);
- communication channel (i.e. unidirectional vs. bidirectional);
- effect on the nervous system (i.e. central nervous system damage vs. denervation).

Pharmacological vs. electrical

This distinction fits with the definition of neuromodulation and leads to two of the main categories for neurodevices namely ''stimulators'' and ''pumps''. In particular, stimulators are devices that use electricity to stimulate the brain, the cord, and the peripheral nerves, whereas pumps refer to implantable devices that inject a pharmacological substance into the nervous system (e.g. baclofen for spasticity or morphine for pain).

Neuroprosthesis vs. neuro-orthosis

In terms of the application of neurotechnology, devices can be categorized to those that couple an artificial system with the physiological system in order to replace or supplement a neuromuscular or sensory function (vision, hearing, tactile), i.e. ''neuroprosthesis'', and are contrasted to those that influence/modulate the neural controller to achieve an ample relief of symptoms of a disease and/or to train the physiological system until the function is performed adequately without any support, i.e. ''neuro-orthosis''. Characteristic type for this kind of devices is the neurostimulation devices.

Therapeutic vs. assistive vs. rehabilitation

Perhaps the most important criterion for distinguishing neurodevices is the purpose of their development, i.e. neurostimulation may be used for muscle contraction to assist in breathing, grasping, reaching, bladder and bowel function. On the other hand TENS (transcutaneous electrical nerve stimulation), does not involve moving muscles, but prevents secondary complications and is aiming at a relief of symptoms (i.e. spasticity, tremor, atrophy).

Yet other devices are applied for rehabilitation, usually after the therapy, and their objective is full restoration or improvement of recovery with some form of training. A third type of device may be complementary to the other two or self-contained and is targeted to supplement, replace or even enhance a function. This type is commonly referred in the literature as an *assistive technology device*. Therapeutic and assistive technology devices may permanently accompany the patient for the rest of his life.

Implantable vs. external

There are two types of implantable devices: one that is completely internal and one with both internal and external components. In the first, the power source (battery) and lead(s) are surgically implanted, whereas in the second a receiver is implanted and detects radio-frequency signals through the skin from an external power source [17]. On the other hand external devices may be ''worn'', e.g. electrodes are attached on the skin and have either a wired or wireless connection to the device [24].

Invasive vs. non-invasive

Devices that require surgery can be implanted at some point in the body and are considered invasive (e.g. deep brain stimulation, DBS) in contrast to those that may operate externally with surface electrodes attached on the surface of the body (e.g. peripheral nerve stimulation, PNS).

Unidirectional vs. bidirectional communication

The human nervous system is a two-way communication system. It has two main types of signals, those that

travel from the brain to the limbs (motor signals) and other signals that go in the opposite direction and carry electrical messages from the limb, trunk, or the head, to the brain (sensory signals). Similarly, there are devices that they have controller units that are able both to send and receive signals. Coupling the human nervous system with electronic and/or robotic prostheses by means of appropriate electrodes ought to permit a bidirectional travelling of signals; from the nervous system to the artificial one (i.e. stimulation) or the opposite (i.e. electrophysiological signal recording). Most important, the user of these devices must be aware of their status and the level of performance, likewise proprioception. Then it is possible to regulate the controller and adjust the parameters to meet the changing conditions. This type of information that the user receives back about the functioning of the device is called biofeedback.

Central nervous system damage vs. denervation

When there is an injury or disease in central nervous system the muscle and its nerve supply remain healthy. In such cases we may replace the natural electrical command signals that originate from the brain with artificial electrical signals that come from a device. External PNS also known as functional electrical stimulation (FES) or functional neuromuscular stimulation (FNS) is a characteristic type of stimulation applied in those cases. For example, peroneal nerve stimulation helps clear the toes during the gait cycle when we have a dropped foot problem in hemiparesis.

When the peripheral nervous system is affected the nerve-muscle connection is broken. This happens in peripheral nerve disorders or injuries and in nerve-muscle diseases. In this case, the central nervous system remains intact but access to the periphery is blocked. Researchers have developed special stimulation equipment to activate denervated muscle directly bypassing the damaged peripheral nerve.

Functional electrical stimulation (FES)

The concept of FES was put forward by Liberson in 1960 for the correction of dropped foot in hemiplegic subjects [15]. Liberson applied FES as an alternative to an ankle foot-orthosis (AFO) to restore functional movement of paralysed muscles. A development of his device the Odstock Dropped Foot Stimulator (ODFS) consisting of "*a single channel, foot switch triggered stimulator designed to elicit dorsiflexion and eversion of the foot by stimulation of the common peroneal nerve*" [24], is widely used in Europe and it started becoming popular in United States [4]. Every FES device is composed by four main components, the electrodes, the stimulator, the sensors or switches, and the leads that connect the electrodes to the stimulator. Currents in the electrodes cause either the weakened or paralyzed muscles to contract or stimulate the tissues without muscle movement. The sensors or switches constitute the interface with the stimulator that controls the strength and timing of the electrical pulses that flow to the electrodes. In FES low level electrical current is applied at specific points of the body to restore or improve function (cardiovascular, bladder and bowel, breathing, grasping and reaching, transfer and standing, stepping and walking, erection and ejaculation, circulation), to prevent or treat pressure sores, contractures, osteoporosis, weak muscles, to control spasticity, tremor, to restore sensation, to regain voluntary function or improve movement control [17]. Apparently FES is not limited to the stimulation of the central or peripheral nervous system, but it is extended to a direct stimulation of muscles (i.e. cardiac pacemaker). In the following paragraphs we describe other subcategories of FES devices according to their primary purpose and effect they have on the nervous system.

Functional neuromuscular stimulation (FNS)

When FES is used to move parts of the body we call it functional neuromuscular stimulation (FNS). FNS operates by stimulating motor nerves as they enter muscles by injecting automated control signals. The contraction of the muscles restores either movement such as limb function, hand grasp, or improves function, such as bowel and bladder operation. Neuromuscular electrical stimulation is also known with the abbreviation NMES. It has shown promise in promoting motor relearning in cases where previously learned motor skills are lost following brain injury, in a stroke for example, by encouraging movement repetition and possibly by promoting cortical reorganization. There are two types of FNS, automatic or synchronous FNS, in which muscles are stimulated to move without conscious effort and EMG-EEG triggered FNS, where the user supplies commands asynchronously. In present days FES systems rely on automated control signals. A neuroprosthetic arm developed in Cleveland FES center [17] is driven by an externally worn joystick on the contralateral shoulder [7].

Neurostimulation devices

The heart pacemaker is considered the first and most renowned application of electrical stimulation. This device applies low level electrical currents to the muscles of the heart to restore the beat rate or improve the beat rhythm. Neurostimulators evolved from cardiac pacemaker technology and use the same principle. In 1963, scientists managed to electrically stimulate and activate the phrenic nerve for long-term artificial respiration [8]. In neurostimulation, electrical stimulation is applied to nociceptive pathways of the central nervous system to modulate pain, spasticity, abnormal movements and seizures in patients suffering from spinal cord and brain injury, cerebral palsy, stroke, epilepsy, and multiple sclerosis. Peripheral nerve stimulation is also used to treat upper/lower extremity nerve problems.

Transcutaneous electrical nerve stimulation (TENS)

If the primary aim of FES does not involve moving muscles, then it may be called simply electrical stimulation (ES), transcutaneous electrical nerve stimulation (TENS), or electrotherapy. In such cases, the primary purpose is to treat the sequellae of spinal cord injury or multiple sclerosis. These include pain, deep venous thrombosis, pressure sores, spasticity, contractures, osteoporosis, atrophy, and tremor.

Peripheral nerve stimulation (PNS)

In PNS, depolarization with electrical current pulses on the surface of the nerve are generated to treat painful paresthesias. PNS has been suggested for the control of chronic intractable neuropathic pain. The most common nerves treated with PNS are ulnar, median, radial, tibial, and common peroneal nerves [23].

Spinal cord stimulation (SCS)

SCS is based on the ''gate-control theory'' of pain. Ionic activity in the cell membranes either opens or closes the pain ''gate''. Accordingly, strategically placed epidural electrodes stimulate the dorsal horns of the spinal column to regulate the flow of nerve impulses from peripherally to the central nervous system (CNS). Implanted spinal cord electrical stimulation was introduced in 1967 by Shealy *et al.* [22]. Therefore, SCS is the oldest and most frequently applied neurostimulation method. There is a significant body of literature on clinical efficacy studies, and the effectiveness has been cross-examined internationally [14, 25].

Sacral nerve stimulation (SNS)

SNS is a surgical procedure in which electrodes are implanted surgically through the sacrum. A small generator device, implanted in the lower abdomen, sends electric pulses that stimulate the sacral nerve, which in turn, stimulates bladder and bowel function. SNS is applied only after less invasive treatments of urge continence have failed. FDA approved SNS device for treatment of refractory urinary urge continence in September 1997. Ontario Health Technology Advisory Committee reports that ''*since 2000, 5 international health and technology assessments (HTA) have been conducted to evaluate SNS. All 5 HTAs reported that SNS was effective*'' [20].

Vagus nerve stimulation (VNS)

In 1997, FDA approved VNS to assist in controlling epilepsy related seizures that are intractable to drug or surgical therapies. In VNS, an electrode is implanted and connected to the left vagus nerve. A generator is placed under the collarbone and is programmed to deliver stimulation of the vagus nerve at set intervals [9].

Deep brain stimulation (DBS)

DBS involves surgical implantation of a multiple electrode lead in the thalamic, pallidal or subthalamic areas of the brain. The leads are connected to an implantable pulse generator (IPG) that is activated by the patient to send a constant stream of electrical pulses to the brain in order to block the tremor [27]. This surgical procedure is used to treat severe essential tremor, rigidity and bradykinesia associated with Parkinson's disease, as well as dystonia and other conditions like depression and obsessive-compulsive disorder. A DBS device designed to control tremors in patients with Parkinson's disease (PD) or essential tremor (ET) was the third type of device approved by the Food and Drug Administration (FDA) in 1997.

Neuropharmaceutical devices

Oral or intravenous medication has the drawback that is diffused throughout the entire body and only a small percentage of the digested substance reaches eventually its final target. By surgically implanting a pump at the precise location where the problem exists, we can pump

medication directly. This drastically cuts down the dose needed, it is often more effective, and it has fewer side effects. There are a lot of alternate infusion routes for certain treatments. Such are intrathecal or epidural spinal pumps that deliver small doses of morphine in the subarachnoid or epidural space [11]. Other types of pumps include intravenous, intra-arterial, subcutaneous, intraperitoneal and intraventricular. The device is surgically positioned in a subcutaneous pocket in the abdominal wall, and a catheter is threaded into the desired position. The period and the volume of the infusion can be adjusted by the physician and the reservoir can be easily refilled with an external needle injection through a self-sealing septum in the pump.

Neuroprosthetic devices

In all aforementioned devices their main distinctive characteristics refer to the type of stimulation (electrical or pharmacological) and the exact position they are inserted. Nevertheless, according to the classification criteria we listed in previously there are other ways we can differentiate neurodevices. Such systems augment, supplement, or complement the nervous system. The term neuroprosthesis was coined to accentuate the interaction and the coupling of the two systems; the nervous and the artificial one. Neural prostheses are devices, which can restore very successfully lost functions resulting from damage to the nervous system. They can take the form of both implanted and externally worn aids to restore many different functions in spinal cord injury and provide patients with remarkable improvements to their quality of life. These devices can be powered and controlled through radio links or have their own in-built power and control. The range of such devices now available to patients is considerable, from vital assistive devices such as heart pacemakers and phrenic nerve stimulators for breathing to multi-channel stimulators capable of restoring useful movements. A neuroprosthetic device shares a lot of common features with neurostimulation devices. They are both considered as artificial control systems with a controller, actuators, mechanics and sensors. This system operates in parallel with the affected part of nervous system. It is mainly the signal acquisition, the type of control, and the interaction that distinguishes neuroprosthesis from neurostimulation. To make a solid point on that terminology issue another frequently term met in the literature review, ''biomechatronics'', is closely related to neuroprosthesis. Biomechatronics focuses on the interactivity of biological organs with electromechanical devices and systems [4]. The primary aim on this field concerns the development and study of artificial hybrid bionic systems and therefore it is not limited to applications such as prosthetic devices. In the sections to follow we summarize systems that have been developed to artificially replace, restore, or augment central sensorimotor control and communication. These can be categorized as artificial prostheses aiming at augmenting functions or substituting parts of the body (e.g. vision, hearing, movement and exoskeletons).

Neurosensor prosthesis (NSP)

Retinal implants

Retinal implants are neuroprosthetic devices that have the ability to restore vision to some extent by converting the light signals to electrical current stimulation on functional neurons in the retina of the eye. Retinal implants are discerned to subretinal, designed to replace photoreceptors in the retina, and epiretinal, designed to communicate directly with the ganglion and bipolar cells. People with degenerative diseases of the retina such as retinitis pigmentosa and macular degeneration may be suitable for treatment. All retinal implants require an intact optic nerve pathway to allow them to function [21].

Auditory brainstem implants

An auditory brainstem implant (ABI) is an implanted electronic hearing aid, designed to generate hearing perception, to a person with severe deafness, by electrically stimulating the cochlear nucleus in the brainstem. The device is composed by an external microphone, a sound processor and an implanted electrode system. The system mimics the inner ear by detecting ambient sounds, digitalizing them and sending them in the form of electrical current through the implanted electrodes a membrane, which contains the electrode contacts and is inserted surgically and applied on the cochlear nucleus surface in the brainstem. Hearing through an implant may sound different from normal hearing, but it allows many impaired people to communicate with oral communication and over the phone [5, 26].

Neuromotor prosthesis (NMP)

The core mechanism of this type of devices is the recording of bioelectrical signals (e.g. EEG, EMG) from the central or peripheral nervous system, and the processing – translation of them into commands for the prosthesis

or other environmental control device. Neuromotor prostheses are now being developed to provide a new pathway or effector between the brain that remains intact and able to generate motor plan, and external devices or paralyzed muscles. There are two types of movement which neuromotor prosthetics must restore: those related to physical movement and those related to communication. The requirements for effective operation are the ability to sense neural activity related to motor plans or actions, the transformation or decoding of this activity into an output signal, and then the coupling of that output to assistive devices or to the muscles as quickly and accurately, as the intact nervous system [6, 7].

In Cyberkinetics, a team of surgeons implanted a 4×4 mm, 100-channel electrode array on the surface of the primary motor cortex (MI) of a 25 year-old quadriplegic ventilator-dependent male. [18]. The surgical procedure consisted of an incision and 3 cm diameter craniotomy to place the sensor in the precentral gyrus immediately posterior to the superior frontal sulcus. Using the BrainGate system the patient gained control of a brain-computer interface and was able to operate the cursor on a computer screen while performing other voluntary motor tasks. NMP relies on the same principle as FNS, both systems attempt to reconnect the brain to the intact neuromuscular system by stimulating motor nerves as they enter muscles, causing the latter to contract. The difference is on the control mechanism of stimulation. FNS is using automated control, thus, it usually sends continuously a signal to the motor nerve while NMP is recording a sufficient residual voluntary movement and transforms it asynchronously into an electrical signal that is fed into the motor nerve for stimulation [19].

Biohybrid systems

The combination of microsystems with biological cells and tissues, known as biohybrid systems, are offering completely new product possibilities for diagnosis and therapy. Microsystem technology is quite new in the field of neural prostheses and will offer solutions where anatomical restrictions in space and the application itself needs a high technical complexity to deliver the adequate performance as it is necessary in a retinal vision prostheses, for example.

Brain computer interfaces (BCI)

Restoring function to those with motor impairments with NMP devices involves providing the brain with a new, non-muscular communication and control channel, to convey commands and messages to the external environment [2, 28]. In the 1970s, Jacques Vidal used the term 'brain-computer interface' to describe any computer-based system that can 'wire-tap' brain activity. Present usage of the term denotes systems that support alternative or augmentative communication and control. BCI is coupling the brain. Instead of the nerves and the motor plan we have computer hardware and software. Electrophysiological signals are the input of BCI and output depends on the type of application (e.g. computer access, environmental control, neuromotor prosthesis control). The two systems, the user and the BCI, interact in a closed loop fashion. During the training cycle, BCI transmits a cue to the user, then it acquires the response as an electrophysiological input from the user, next it translates the signal into output to control a device. When user-intended command is executed the individual receives a type of feedback through the sensors about the resulted action. The consequence of this is that the user in turn adapts to the BCI by modifying the response and the BCI should adapt according to the learning ability of the user by increasing the level of practice. Successful operation of the BCI is the result of adequate adaptation of each system through the use of feedback.

Similarities of assistive technology with the neurodevices

Assistive technology is defined in the Technology-Related Assistance Act (Tech Act, 1988) as "*any item piece of equipment, or product system, whether acquired commercially off the shelf, modified, or customized, that is used to increase, maintain, or improve functional capabilities of individuals with disabilities*". AT may improve the physical or mental functioning of the disabled, enable them to accomplish daily living tasks, assist them in communication, education, work or recreation activities. In other words help them achieve greater independence and enhance their quality of life. One can immediately realize that AT and Neurotechnology share a common objective which is to help the individual to overcome a disability or impairment.

When AT is divided into categories or product families, one can notice the similarities with neurodevices taxonomy. In particular prosthetics and orthotics, vision and reading aids, hearing and listening aids, include both neurotechnology and non-electronic equipment that assist the disabled. More specifically Augmentative Alternative Communication (AAC) is built around the concept of communication of the impaired individual

with the environment. AAC involves alternate methods of communication through the use of electronic and non-electronic devices for the disabled. It includes communication boards, text-to-speech software, speech recognition software, head wands, mouth sticks, signal systems, and others.

In two other categories of AT namely environmental control systems (ECS), and computer access aids, applications of the brain computer interface are commonly included. ECS enable someone with limited mobility to control various electrical appliances. Computer access aids include alternative input and output devices together with adapted software applications that enable persons with disabilities to access, interact with, and use computers.

Technical and biological complications

Three decades of continuous development of implanted devices and technological progress make operative techniques safer, and the equipment implanted more robust. Nevertheless there are both technical and biological complications that arise from their use. For instance, spinal cord stimulation devices have been examined and studied extensively for more than thirty years. In a recent literature review, researchers report that the most common problems with the operation of the device are: lead migration, lead breakage, over- or understimulation, loose connection, battery failure, hardware malfunction. In addition, biological complications include infection in the tissues surrounding the implant, cerebrospinal fluid leakage, and pain at the incision electrode or receiver site [3]. In the same review, it is most encouraging to notice that the percentage of incidence of these cases is very small compared to the total number of patients with an implanted device.

Another characteristic example of technical complication is the type of interaction of the user with the neurodevice. In certain functional electrical stimulation operated devices the stimulation is handled automatically for safety reasons. Conscious intervention from the user to handle the operation of the device is a highly complex task. ''*To accomplish this, the device must be able to detect specific brain activity at any time a command is intended, and disregard all other brain activity that arises when the user is performing other tasks*'' [1].

Many devices need adjustments; if the surgeon or the clinician is new to the device she/he must receive guidance from a qualified engineer for this type of devices. That simply means that the surgeon must be interested and even skilled at implanting and using the device [5]. Another complication regards insurance and indemnification. In feasibility and/or clinical trial studies, the physician has to examine whether the patient is covered by his or her insurance for injury claims, device malfunction, or even death resulting from faulty equipment and the extent of liability of the manufacturer [5].

Embracement of neurotechnology in the medical profession

In 1998, Health Technology Advisory Committee (HTAC), reviewed neurostimulation devices and found that [12]:

i. There are not large-scale clinical trials published in medical literature.
ii. Devices are appropriate for a small number of patients compared to the total number of patients with a disorder. This is due to the fact that there are strict criteria based on various assessment tests that include or exclude a patient from a clinical trial.

In United States gaining FDA approval may take years. Safety and effectiveness of the device is tested on a large group of subjects in order to gather sufficient information from multicenter clinical trials. This is one of the main reasons that today many neurotechnology devices are investigational. Moreover, even if it is approved by FDA, clinicians will reach a ''consensus'' in many years to accept them in their practice. That means the clinical availability of the device may be restricted or limited in only a few clinical research centers around the world [17]. Other reasons that prohibit the embrace of this technology in the medical profession include technical problems, poor documentation and training for the practitioners and absence of continuous development [24].

Financial implications

Neurotechnology is an expensive complex technology for many reasons; treatment is usually very specialized, it is a new technology in the medical marketplace and the cost of the components of the devices is substantial. The battle for dominance of neurodevices over neuropharmaceuticals is enduring. Evidence presented in the review from Taylor *et al.* showed that the actual cumulative cost for SCS treatment of chronic pain incurred in diagnostic imaging, implantation, hospitalization, physiotherapy, maintenance of the stimulator, for a 5-year period is economically favorable in comparison to best conventional pain therapy method but in the first two

years the cost is significantly more for SCS [25]. More important, in a similar study by Kumar *et al.* an assessment of the SCS group indicated a 27% improvement in quality of life compared with 12% improvement for the control group. In addition, 15% of SCS-treated patients were able to return to employment but none was able to return to employment from the control group [14].

Future prospects

There are 1.5 billion people worldwide that suffer from neurological diseases and psychiatric illnesses, the largest and fastest growing medical sector [16]. Until recently, stimulation methods were usually the last resort, when patients were intractable to medical and other non-invasive treatments or when other more conservative therapies had proved ineffective in addressing a particular condition. As the technology advances, implantation technique is simplified, devices are miniaturized, durability and reliability is prolonged, and effectiveness is increased while side-effects are decreased. Despite all these improvements, Neurotechnology is still at an infancy stage and progress resembles the adoption and development path of cardiac pacemakers. "*Systems now in use rely on rather gross levels of electrical stimulation, placement is relatively imprecise, and control parameters are empirically derived*" [3]. In the same article, the authors report that "*these devices are not modulated by feedback sensed by the system, are always "running" and require subjective human intervention for calibration due to changes in the patients state*". Neurostimulation or neuroprosthetic devices will become more practical when their operation will be adjusted automatically according to changes in the environment or in the user's body. One can arguably say that the perfect device is the one that the user will feel like any other part of his body. At the present the main reason that stimulation is optimized empirically by trial-and-error is due to our limited knowledge about the underlying biophysical mechanisms. The development of new generation devices will require computer modeling of electrical stimulation of nerve fibers, the neuronal target area, and the surrounding anatomical structures.

Conclusion

Man is the undisputable ruler of planet earth. We survived and we evolved thanks to the technology we developed. Nevertheless the ever-lasting battle on human mortality and diseases has not been conquered yet. Neurotechnology is our latest weapon to fight against the suffering from our bodily weakness, to prolong our life, and to expand our physical or mental ability. This is the time where science fiction has started to become reality. But there is always this tormenting question that emerges when we compare ourselves against other artificial or physical forms of life. What makes us humans? Is it our brain – mind or perhaps is it our body – soul?

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Management of chronic severe pain: spinal neuromodulatory and neuroablative approaches

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Summary

The spinal cord is the target of many neurosurgical procedures used to treat pain. Compactness and well-defined tract separation in addition to well understood dermatomal cord organization make the spinal cord an ideal target for pain procedures. Moreover, the presence of opioid and other receptors involved in pain modulation at the level of the dorsal horn increases the suitability of the spinal cord.

Neuromodulative approaches of the spinal cord are either electrical or pharmacological. Electrical spinal cord modulation is used on a large scale for various pain syndromes including; failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), neuropathic pain, angina, and ischemic limb pain. Intraspinal delivery of medications *e.g.* opioids is used to treat nociceptive and neuropathic pains due to malignant and cancer pain etiologies.

Neuroablation of the spinal cord pain pathway is mainly used to treat cancer pain. Targets involved include; the spinothalamic tract, the midline dorsal column visceral pain pathway and the trigeminal tract in the upper spinal cord. Spinal neuroablation can also involve cellular elements such as with trigeminal nucleotomy and the dorsal root entry zone (DREZ) operation. The DREZ operation is indicated for phantom type pain and root avulsion injuries.

Due to its reversible nature spinal neuromodulation prevails, and spinal neuroablation is performed in a few select cases.

Keywords: Neuromodulation; chronic pain; spinal; neuroablation; treatment.

Introduction

Surgical targeting of the spinal cord to control pain was first reported in the early twentieth century by Spiller and Martin, who in 1912 performed an anterolateral section of the spinal cord to treat pain in the lower body [66]. From that time, the concept of sectioning pain pathways in the spinal cord has been widely employed and has involved several targets including; the spinothalamic tract, the midline crossing commissural pain fibers in front of the spinal cord central canal, the extralemiscal multisynaptic ascending visceral pain pathway, the dorsal root entry zone and the trigeminal tract in the upper spinal cord, and the medulla [1, 24, 26, 27, 48, 61, 62, 65]. Several methods have been used to interrupt pain transmission including; knives, radioactive strontium needles, and electric current and radiofrequency (RF) both via open and percutaneous procedures with either high or low cervical approaches [11, 20, 42, 46, 47, 60, 68].

With the introduction of gate theory by Melzack and Wall in 1965, which described the role of the dorsal horn in regulating pain transmission, the concept of neuromodulation via electrical stimulation of the spinal cord was introduced, as was the concept of pharmacological neuromodulation [45].

Details describing the distribution of opioid receptors in the dorsal horn and in several locations along the brain stem, along with reports describing the descending endogenous mechanisms for modulation of pain perception paved the way for the use of intrathecal drugs to treat chronic pain. Opioids by far constitute the most widely used drug [7, 9, 51].

Spinal neuromodulation methods used to control severe chronic pain are spinal cord stimulation (SCS) and chronic intrathecal drug administration. Spinal neuroablative procedures include; cordotomy, myelotomy, trigeminal tractotomy, and dorsal root entry zone (DREZ). The wide spread use of neuromodulation methods substantially decreased the use of neuroablative procedures performed globally, however spinal neuroablative procedures remain indicated for particular pain conditions.

The advantage of neuromodulation procedures over neuroablative is reversibility and safety. In an environment

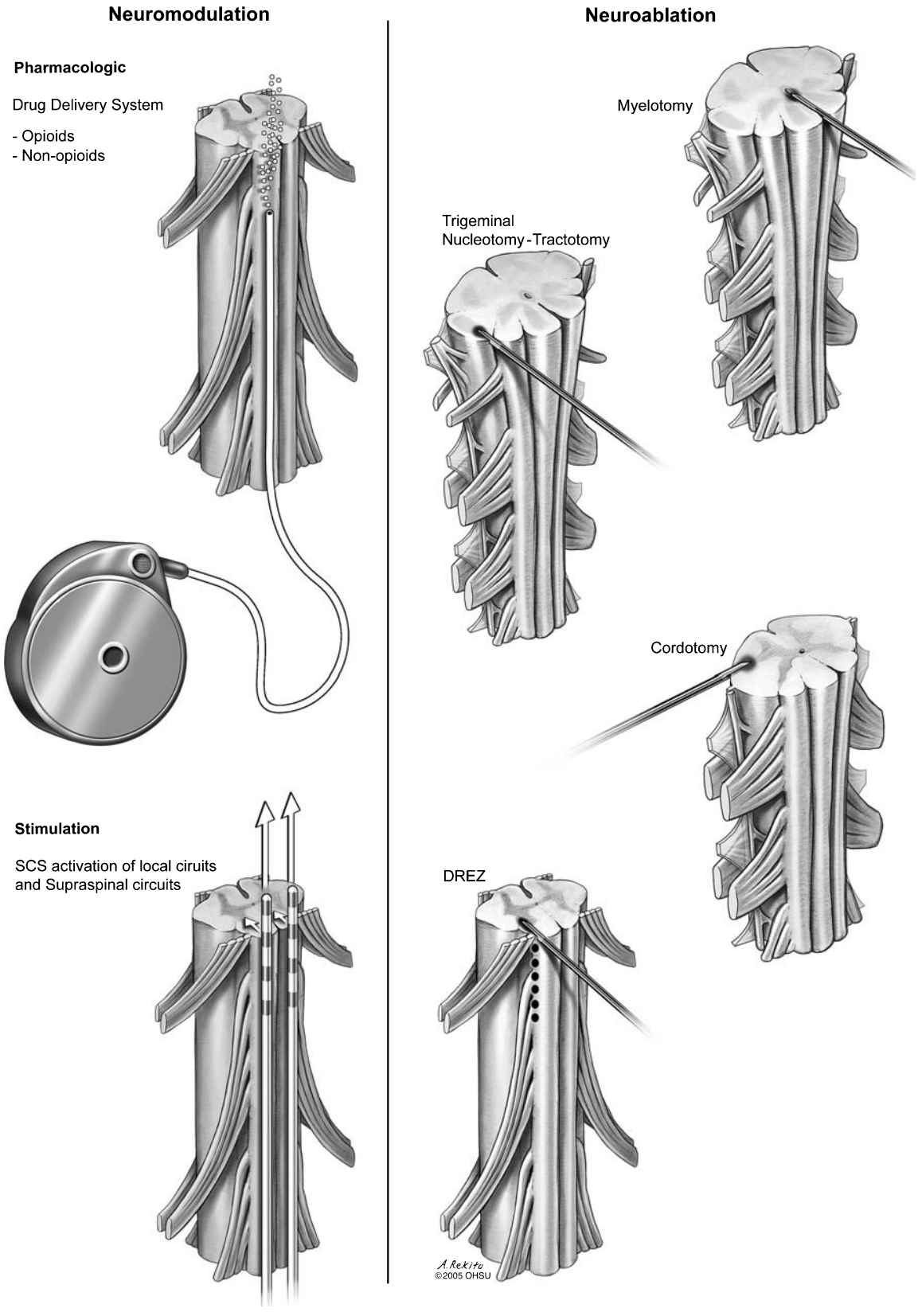

Fig. 1. Diagrammatic representation of spinal neuromodulation and neuroablation procedures

of scientific discovery with evolving concepts and techniques, it is imperative to avoid destructive non-reversible procedures, especially when treating patients with benign pain syndromes (Fig. 1).

Spinal neuromodulation

Spinal cord stimulation

The first spinal cord stimulation procedure was performed by Shealy *et al.* in 1967 and was a direct gate theory spin-off. These investigators placed an intradural electrode onto the dorsal surface of the spinal cord to treat cancer pain. Simply, the thought was to stimulate the easily accessible neural structures and activate 'the gate'. Electrodes were first placed subdural, followed by intradural, followed by epidural, with the aim of stimulating the dorsal part of the spinal cord, hence the name, dorsal column stimulation [63].

Despite a plethora of publications detailing SCS the precise mechanism of action remains unclear. Initially, it was speculated that the pain-relieving effect of SCS could be explained as inhibition of nociceptive impulses at the dorsal horn resulting from the stimulation induced activation of large dorsal column fibers. However, later it was evident that this simple explanation was insufficient. There are both electrical and pharmacological changes along the whole segment of the spinal cord being stimulated, hence the name change to spinal cord stimulation [43]. Several mechanisms of SCS action, mostly derived from observations related to the conditions that SCS has been used successfully to treat, have been proposed.

Suppression of the hyperexcitability of wide dynamic range neurons in the dorsal horn is one such suggested mechanism. Others include; suppression of high threshold nociceptive-specific spinothalamic neurons by dorsal column stimulation [10], and activation of inter-neuron networks near or in the substantia gelatinosa, which in turn inhibit the deeper lamina III-V in the dorsal horn [14]. All are possible mechanisms at interplay during SCS. Supraspinal mechanisms are also activated. The anterior pretectal nucleus can be excited by SCS, which in turn produces profound analgesia by inhibiting the nociceptive dorsal horn neurons. Furthermore this effect can out last the stimulation of certain parameters. The long-lasting effect of SCS is thought to be mediated via the dorsolateral funiculus because sectioning this tract abolishes the long-lasting effect [59].

Spinal cord stimulation activates gamma-aminobutyric acid_B ($GABA_B$) receptors, which suppress the exaggerated excitatory amino acids in dorsal horn cells. The supraspinal mechanisms operating during SCS induce the release of the neurotransmitters glycine, adenosine and 5-hydroxytryptamine (5-HT). The described electrical and chemical changes that occur as a result of SCS can explain its efficiency in treating neuropathic pain types. For ischemic pain the mechanism of SCS action differs. There are many postulated mechanisms, the most accepted of which is that of modulation of autonomic activity theory, in which rebalance of oxygen demand and supply is the cause of pain relief. This mechanism of action can also describe the effects of SCS on angina pectoris [43].

During stimulation of a spinal cord segment, patients feel paresthesia over the body part that corresponds to the spinal cord segment being stimulated. Ideally, paresthesia should not be due to dorsal root dermatomal stimulation, therefore a midline or near midline electrode placement is advisable. Stimulation paresthesia is considered by physicians involved in the field of SCS as a hallmark of success. Perception threshold is the minimal voltage at which the patient starts to perceive paresthesias. This threshold is in part a function of the thickness of the cerebrospinal fluid layer dorsal to the cord; therefore perception threshold is lowest in the cervical area and highest in the midthoracic area.

There are several SCS system manufacturers. Systems are generally composed of electrode(s), either percutaneous or plate, and a pulse generator or radiofrequency (RF) receiver. Plate electrodes require an open placement approach and are permanent in nature. To allow for complex programming/stimulation of spinal cord segments there are different electrode designs, some with up to 16 contacts in a single electrode. Electric power is delivered through either a completely permanent system, a ''pulse generator'' or a RF coupled generator and an implantable receiver.

First generation SCS electrodes were unipolar and attached to a power source that could not be programmed following implantation. However, in the last decade, and with technological advancements, octapolar electrodes (and even higher number electrodes) are now available together with dual channel programmable power units, and most recently, rechargeable units.

The implantation procedure usually requires a trial period with a percutaneous electrode that allows for time to judge the benefit of stimulation, followed by a permanent system implantation, if the trial period is successful. A successful trial is usually one whereby the patient experiences more than a 50% reduction in pain.

Psychological screening is helpful in selecting candidates for SCS [6].

In the last 30 years several studies have assessed the overall clinical efficacy of SCS when used to treat various chronic benign pain conditions. Failed back surgery syndrome (FBSS), which encompasses many different types of pain in several locations including; midline axial and limb pain, and neuropathic and nociceptive components, is the most common indication for SCS. Barolat *et al.*, Burchiel *et al.*, and North *et al.*, all performed well designed clinical studies to assess SCS for FBSS. They reported favorable outcomes for SCS on the limb and neuropathic pain component of FBSS with successful pain reduction of more than 50% (range 55–88%). For several reasons the midline axial component of FBSS is more difficult to treat with SCS, however, recent reports have examined the possibility of treating back and limb pain using SCS [5, 8, 53].

Complex regional pain syndrome (CRPS) encompasses a wide range of clinical symptoms, is difficult to treat, and is the second most common indication for SCS. Several studies have confirmed the efficacy of SCS in treating CRPS. There is a tendency to utilize higher frequencies to control pain in CRPS, also if multiple limbs are involved, patients may need multiple electrode implantations in the cervical and lower thoracic areas to achieve pain control. In 2000 and 2002, Kemler *et al.* conducted a well-designed randomized controlled trial comparing SCS and physical therapy to physical therapy alone. The investigators assessed patients at 6 and 12 months follow-up and reported a statistically significant but clinically modest difference between the two groups, with the SCS and physical therapy group reporting a higher degree of pain relief [38, 39].

Angina pectoris shows promise as an indication for SCS and many studies have uniformly reported good results. The mechanism of pain reduction, as mentioned earlier, is postulated to be due to nociceptive signal blockade together with secondary gain due to decreased ischemia as a result of improved oxygenation [44]. Yu *et al.* performed a retrospective analysis of 24 patients and showed that SCS was effective in improving quality of life, number of hospitalizations, treatment costs, and physical abilities [78].

Chronic critical limb ischemia is also an emerging indication for SCS, particularly in Europe however, falls beyond the interest of this chapter. Phantom limb pain, postherpetic neuralgia and spinal cord injury pain have all been treated by SCS but with less favorable outcomes when compared to FBSS, CRPS and angina pectoris.

Complications resulting from SCS are generally non life-threatening and reversible. In the well-designed systematic review of SCS reported by Turner *et al.*, complications across studies included in the review included; deep and superficial infection (mean infection rate 4.5%), pain at the site of implantation (mean pain rate 5.9%), biological complication other than infection or pain occurred in 2.5% of patients, equipment failure was reported in 10.2% of patients, stimulator revision for any reason other than changing the battery in 23.1% of patients, and stimulator removal in 11% of patients [70]. Neurological deficits due to SCS technique or due to unexpected epidural bleeding are extremely rare [18].

Neuromodulation via intraspinal delivery of medications

Intraspinal narcotics

The use of intraspinal delivery of narcotics continues to grow and now includes treatment of chronic non-malignant pain as well as cancer-related pain.

Discovery of spinal cord opioid receptors first initiated the use of intraspinal narcotics to treat chronic malignant pain etiologies and grew to include treatment of chronic non-malignant pain conditions. Direct morphine delivery to spinal cord mμ opioid receptors can decrease the amount of morphine that may be required to achieve an equianalgesic effect [73].

Intraspinal narcotic action was first appreciated in 1976 when Yaksh and Rudy applied several different opioid compounds to the subarachnoid space of awake rats. In this study hind-limb withdrawal to noxious stimuli attenuated soon after a bolus administration of opioids to the subarachnoid space [77]. Intraspinal opioid administration produces a direct inhibitory action on dendritic cells, or is thought may act on modulatory interneurons to produce a decrease in the central transmission of nociceptive impulses [75, 76]. Nonetheless, treatment of neuropathic pain with intraspinal morphine in animal models has been demonstrated to be effective. It is possible that treatment of human neuropathic pain may require higher doses of intraspinal opioids and eventually non-opioid intraspinal drugs may prove more effective [40].

Treatment of human neuropathic pain with intraspinal opioids remains a viable option. Of paramount importance is the patient selection process and in the last decade there have been changes in determining the best candidates. Typically, the patient selection process relies on factors like; (1) pain type, with preference of

nociceptive somatic pain without exclusion of other pain types, (2) pain distribution, with a preference of axial and diffuse rather than focal limb pain, and (3) the presence of a favorable response to intraspinal opioid trial (currently the gold standard in the process of patient selection) [41]. Nociceptive somatic pain due to cancer pain has historically been viewed as the ideal indication with little non-cancer pain being treated with intraspinal narcotics. However currently, the number of non-cancer pain patients being treated by intraspinal narcotics may outnumber the cancer pain patients [55].

The opioid pump implantation process can be performed under local anesthesia or more commonly under general anesthesia. Several commercial catheters and drug delivery pumps are available, and include programmable and constant rate infusion pumps.

The literature consistently reports between 60–80% improvement in pain for various indications. For non-malignant pain an average improvement of 60–65% is reported [4, 17, 22, 23, 54, 58].

Unfortunately, the downside of this effective procedure are the numerous and on rare occasion, life-threatening complications. Complications are either system or procedure related and include; wound infection (either superficial or deep), seroma formation, meningitis or epidural abscess, spinal headache, catheter migration, kink or breaks in the catheter, and pump malfunction due to rotation or rarely mechanical failure. Drug related complications include; constipation, urinary dysfunction, nausea, impotence, vomiting, nightmares, pruritis, sweating, weakness, edema, weight gain, paradoxical hyperalgesia, morphine withdrawal, which can be serious, and sedation [54, 74].

Intraspinal neuromodulation with non-opioid drugs

Despite the widespread use of intraspinal opioids and the continuous expansion of indications coupled with the impact on neuroablative procedures, several side effects and inefficiencies remain. Additionally, intraspinal narcotics are not suitable for every patient, and drug tolerance and increased need for opioid over time, all constitute a rationale for development of innovative non-opioid therapies for intraspinal use.

The following are the latest non-opioid agents proposed for intraspinal delivery via an implanted drug administering device; (1) clonidine, (2) octreotide, (3) neuronal-specific calcium channel blockers (Ziconotide), (4) N-methyl-D-aspartic acid (NMDA) antagonists (dextromethorphan, dextrophan, MK-801, 5-Neostigmine), (6) benzodiazepines, (7) butamin, (8) bioactive implants (matrix adrenal medullary cells), (9) tricyclic antidepressants, (10) nitric oxide synthetase inhibitors, and (11) liposomal encapsulation of local anesthetics [19].

The use of non-opioid drugs is at the frontier of the field of pain management treatment and further research certainly holds future promise.

Spinal neuroablation

The first surgical disruption of spinal pain pathways was performed by Spiller in 1912. Spiller sectioned the anterolateral quadrant of the spinal cord, with the intention of interrupting pain transmission via the spinothalamic tract and relieving pain in one side of the body [66]. For many years this open procedure of sectioning the spinothalamic tract for pain control was a standard procedure in many neurosurgical centers and was used mainly to treat somatic nociceptive pain. The main issues related to these open destructive spinal cord procedures were, the poor general status of the cancer patients in tolerating open spinal cord surgery together with high complications profiles.

A percutaneous approach to the spinal cord was first introduced by Mullan and Rosomoff in the late 1960's [46, 47, 60] and the approach was adopted by most neurosurgeons. However, since the early 1990's with the introduction of neuromodulative therapies including chronic administration of spinal opioids and SCS for pain, spinal ablative procedures are now rarely performed.

In an era of spinal neuromodulation to treat pain, two noteworthy developments have resurrected interest in the use of neuroablative procedures to treat pain. One is the introduction of a computed tomography (CT) guidance method that drives an electrode into spinal cord pathways, and allows for precise visualization of the electrode-target relationship [33]. The second is the introduction of the dorsal root entry zone (DREZ) as a potential site for ablation to treat deafferentation pain [50].

Possible neuroablation spinal cord targets to treat pain are; (1) spinothalamic tract, ablated to treat somatic nociceptive pain below the level of the neck, *i.e.* cordotomy, (2) trigeminal spinal nucleus, ablated to treat neuropathic and resistant facial pain, *i.e.* trigeminal tractotomy-nucleotomy, (3) the midline ascending visceral pain pathway in the central part of the spinal cord, to treat visceral pain around the midline, *i.e.* midline myleotomy, (4) DREZ, ablated to treat deafferentation pain (Fig. 1).

Cordotomy

Cordotomy refers to lesioning or interrupting the lateral spinothalamic tract (LST) located in the anterolateral quadrant of the spinal cord. Historically, surgery was performed in the upper thoracic spine using an open posterior approach and high cervical cordotomy was first reported in 1927 [29].

The spinal cord anterolateral ascending pain transmission system carries information mostly about pain and temperature from one side of the body and decussates the spinal cord (from two up to five segments higher than the level of entry into the spinal cord) to carry the signals to the thalamus and cortex. Fibers in the LST have a somatotopic arrangement with sacral segments posterolaterally and cervical segments anteromedially [71]. The pyramidal tract lies posterior to the LST with white matter in between. The ventral spinocerebellar tract overlies the LST and a lesion that eliminates the spinocerebellar tract may cause ipsilateral ataxia of the arm.

Human autonomic pathways for vasomotor and genitourinary control in addition to the reticulospinal tract that controls ipsilateral automatic respiration are also part of the anterolateral quadrant of the spinal cord. Therefore sleep apnea, incontinence and hypotension are possible undesirable effects of cordotomy.

The ideal candidate for a cordotomy procedure is a patient with cancer pain of a somatic nociceptive nature that is localized below the neck and to one half of the body [37].

From the beginning of the 20th century until the late 1960's/early 1970's, cordotomy was an open procedure, one which presented a challenge to already debilitated patients. However, because it was an open procedure it was possible to perform at different levels including higher thoracic levels, thus avoiding complications such as ataxia and sleep apnea [28]. The introduction of a percutaneous approach by Mullan and Rosomoff altered the magnitude of risk and side effects, and made it possible for the procedure to be performed on patients of poor general condition, *i.e.* the majority of cancer pain patients [46]. Several authors and many neurosurgeons adopted the percutaneous approach; however, in the mid 1980's and early 1990's, advances in opioid pharmacology as well as the introduction of reversible neuroaugmentative techniques lead to a major reduction of the number of cordotomies performed worldwide.

The downside of a percutaneous cordotomy is the possibility of developing sleep apnea when the lesion is performed in the higher cervical region, and the possibility of under-lesioning the cord leading to improper pain control [37].

Kanpolat first introduced the concept of CT guidance, which allowed for a safe, easy and selective cordotomy [30, 31, 36]. In 1995, Fenstermaker [16] performed anterior CT-guided lower cervical cordotomy through the disc to avoid sleep apnea (a modification of Gildenberg's anterior low cervical percutaneous cordotomy [20]). In a recent clinical study anterior CT-guided cordotomy was used to control cancer pain in six of eight patients with pulmonary-pleural malignancy, to avoid sleep apnea; follow-up period was six months [57].

Today's cordotomy procedure involves lumbar puncture and injection of a water soluble dye into the patient's intrathecal space, 30 minutes prior. A CT scan directs guidance of a cordotomy electrode, which is isolated throughout the entire shaft excepting the tip (2 mm in length and 0.3–0.4 mm in diameter). After measurement of skin-dura distance an electrode is introduced from the lateral side of the neck opposite the C1–C2 foramen in the anterolateral quadrant and with guidance the electrode can produce selective lesions. To assure complete entry into the spinothalamic tract (avoiding the corticospinal tract), electrophysiological testing is essential. Lesions are performed until adequate hypoesthesia is achieved in the contralateral hemi-body or at least in the region of pain. CT-guided cordotomy has a higher success rate compared with image guided cordotomy, and fewer side effects. Cancer pain control is reportedly greater than 95%.

Cordotomy procedure complications include; weakness, hypotension, dysesthesia, mirror image pain, ataxia, incontinence, and sleep apnea. Today's CT-guided cordotomy complications tend to be minimal and transient [34].

Trigeminal tractotomy-nucleotomy

Fifth, seventh, ninth and tenth cranial nerve sensory information is carried by the trigeminal tract and branches into the trigeminal tract spinal nucleus extending caudally into the spinal cord to C2 [67]. The trigeminal tract was considered a target for treating facial pain early in the development of utilizing pain pathways to treat pain surgically [65], and similarly to cordotomy, tractotomy procedure development followed a progressive course. Crue and Hitchcock developed a stereotactic technique to lesion the trigeminal tract and the nucleus using radiofrequency [12, 26]. Later, and to emphasize the significance of creating lesions in the oral pole of the nucleus

caudalis, Hitchcock named the procedure trigeminal nucleotomy [49]. Similarly to CT cordotomy, the trigeminal tractotomy-nucleotomy (TR-NC) procedure utilized today is performed with CT guidance.

Trigeminal tractotomy-nucleotomy indications include; anesthesia dolorosa, postherpetic neuralgia, neuropathic facial pain, facial cancer pain, and glossopharyngeal and geniculate neuralgia [32, 35].

CT-guided TR-NC pain relief is reported as complete or satisfactory in 80% of cases. Complications include; ataxia due to injury of the spinocerebellar tract (currently, rare and temporary), and contralateral hypoalgesia, if the spinothalamic tract is included in lesioning [26, 32, 35, 69].

The nucleus caudalis dorsal root entry zone (DREZ) operation, involves the same concept as the TR-NC procedure but includes destruction of the whole substantia gelatinosa of the nucleus caudalis.

Extraleminscal myelotomy

The intention of the extraleminscal myelotomy (ELM) procedure is to create a lesion in the central medullary region at cervicomedulary junction. The procedure was first described by Hitchcock, who aimed to destroy the decussating fibers of the spinothalamic tract to control pain in the neck and both arms [25]. It was soon realized that ELM controlled pain below the expected level of the lesion and hence, Schvarcz added 'extraleminiscal' to myelotomy anticipating that the target was an ascending non-specific polysynaptic pathway [61]. In the last decade, many authors have confirmed the presence of such a tract and performed midline punctuate myelotomy through open procedures to lesion the pathway at various spinal cord levels. The multisynaptic ascending pathway is thought to carry visceral nociceptive impulses and lie deep in the midline dorsal column [2, 3, 52].

The concept of CT guidance applied to cordotomy and TR-NC procedures applies to ELM; again, Kanpolat pioneered the ELM procedure used today [32].

Extraleminscal myelotomy indications include; patients with pelvic malignancy or cancer pain in the lower trunk and lower extremities with a predominant visceral pain component. The procedure is safe, however, pain relief results are not as high as those achieved with cordotomy and tractotomy nucleotomy procedures [29].

Dorsal root entry zone surgery

The introduction of gate theory in the 1960's drew attention to the dorsal horn as a level for pain modulation [45], and the dorsal horn was then considered by neurosurgeons as a target of either neurostimulation, SCS, or neuroablation of the DREZ.

In 1972, Sindou [64] first attempted DREZ destruction followed by Nashold *et al.* who introduced radiofrequency to perform DREZ lesioning [51]. More recently, laser beam and ultrasound probes have been used [13, 56].

The anatomophysiological basis of the DREZ derives from the fact that when the large leminiscal afferents in peripheral nerves or dorsal roots are altered, there is a reduction in the inhibitory control of the dorsal horn [72]. This situation presumably results in excessive firing of the dorsal horn neurons and this phenomenon is thought to be the cause of deafferentation pain and hence able to be controlled by DREZ lesioning [21].

The technical details of the procedure and its variants are beyond the scope of this chapter but DREZ lesioning is performed as an open procedure using general anesthesia and often times accompanied by intraoperative neurophysiologic monitoring.

Candidates for the procedure are patients with; brachial plexus avulsion, pancoast tumor with brachial plexus invasion and good general condition and long life expectancy, pain due to spinal cord or cauda equine lesions, postherpetic neuralgia, peripheral nerve injury pain, and pain accompanying hyperspastic states [64].

When patients are carefully selected and the lesions accurately performed the success rate can be as high as 90% (with follow up reported of up to 4 years). Complications and side effects include; CSF fistula, meningitis, ataxia, increased neurological deficits, and dysesthesias [15].

Conclusions

The spinal cord has proved to be an excellent target for pain control, specifically due to compactness and the luxury it affords for performing both neuromodulation and neuroablation techniques.

Spinal cord stimulation and intraspinal drug delivery systems constitute the majority of neurosurgical procedures used today, to treat chronic pain, and are indicative of the crucial role played by the spinal cord.

However, further evidence is required regarding the precise indications for SCS and there is a need to explore additional drugs for intraspinal administration to treat pain.

Spinal neuroablation remains an option and is indicated for particular pain syndromes especially those conditions involving cancer pain.

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Intrathecal opioids for intractable pain syndromes

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Summary

For more than 20 years intrathecal opioid application with implantable pumps is an option for selected patients with malignant as well as non-malignant pain. In general, most types of pain should be treatable by opioid medication. However, the associated systemic side-effects such as nausea, vomiting, constipation or the risk of suppression of the central nervous system hinder the application of oral or intravenous opioid therapy as a sole, widely applicable treatment. Causes of non-malignant pain that may represent an indication for intrathecal drug-delivery systems include: failed back syndrome, neuropathic pain, axial spinal pain, complex regional pain syndrome, diffuse pain, brachial plexitis, central pain, failed spinal cord stimulation (SCS) therapy, arachnoiditis, poststroke pain, spinal cord injury pain and peripheral neuropathy. Due to the proximity to the receptor sites, the therapeutic effect of intrathecal drug application lasts longer and the rate of systemic side effects is reduced. Before definitive pump implantation, the therapeutic effect of intrathecal opioid therapy is tested with an external pump. If there is no clear and satisfactory effect in this trial application, pump implantation is not indicated. In our patients, with a follow-up exceeding 3 years, the reduction of non-malignant pain (assessed with the Visual Analogue Scale, VAS) was good or excellent (pain decrease >50%) in 71.3% of the patients, fair (VAS 5–6) in 19.8% and poor (VAS 7–10) in 8.9%. After 3 years of continuous treatment, we observed catheter-related technical problems (catheter dislocation, obstruction, kinking, disconnection or rupture) in 17 of 165 patients. Pump malfunctions were very rare (8 of 165 cases) and limited to older pump types. Reversible, specific drug-related side effects of long-term therapy with intrathecal pumps developed in 32 of the 165 patients. In our series, the mean serum/cerebrospinal fluid (CSF) concentration ratio for morphine was 1/3000, which explains the low rate of systemic side effects. Local diffusion difficulties in CSF cause an uneven distribution of morphine in CSF. Therefore the clinical effect is markedly influenced by the position of the catheter tip, a fact that should be kept in mind during catheter implantation.

Intrathecal drug application is cost effective and can significantly improve the quality of life in selected patients. An intensive training in this method and awareness of its specific complications is necessary for everyone to participate in the consulting and implanting team. Pumps for chronic intrathecal opioid application should only be implanted in specialized centers.

Keywords: Catheter; chronic; drug; implantation; intrathecal; metabolism; morphine; neurosurgery; pain; pump.

Introduction

The advantage of intrathecal drug application is the vicinity to the receptor site. Compared to systemic intravenous application, the therapeutic effect is longer lasting, is achieved with a smaller dose, and therefore is associated with a reduced rate of side effects [1, 8, 16, 18, 22, 27]. Intrathecal opioid therapy was initially introduced for malignant pain. In general, the pain should be sensitive to opioid medication, but due to increasing systemic side-effects such as nausea, vomiting, constipation or central nervous system depression, oral or intravenous opioid therapy alone is no longer acceptable. The targets of intrathecal drug application are the pre- and postsynaptic receptors in the dorsal horn of the spinal cord. Bernards *et al.* [6] have shown that intrathecal morphine application has not only a direct central effect, but also significant systemic effects due to dural penetration and local absorption. Currently, epidural analgesia for obstetrical, postsurgical and cancer-related pain is very common, but also intrathecal opioid therapy is increasingly used [3–5, 9, 19, 20]. The choices of analgesic agents include opioids, alpha-2-agonists, and local anesthetic agents [2, 7, 30]. The disadvantages compared to intravenous drug applications are relatively high costs and potential complications such as meningitis and catheter dislocation. To minimize such risks, intrathecal opioid drug application with implantable pumps should be performed by interdisciplinary teams in specialized centers. Before implanting a pump for continuous drug application, the therapeutic effect of intrathecal application should be assessed by a bolus trial or continuous injection via an external pump, connected to the intrathecal catheter through an implanted port. Placebo phenomena may

interfere with the effects of a bolus injection, but continuous intrathecal infusion is much more reliable in assessing and predicting the long-term therapeutic effect.

When comparing epidural with intrathecal drug application, one should consider that in epidural application higher doses of the drug are required, and the systemic side effects can be more pronounced. Certain side effects are the result of absorption of the drug into the venous circulation. Catheterization of the epidural space for drug application may be more difficult when compared to the intrathecal procedure. On the other hand, the placement of an intrathecal catheter carries a higher risk of catheter dislodgment, root irritation and reactive arachnoiditis in chronic application. In general, spinal drug application is indicated when the pain syndrome responds to opioids but not to oral medication and there is no indication for surgical therapy (spinal decompression, disc surgery etc) after a full diagnostic work-up. Patients suffering from psychiatric disorder or drug addictions should be excluded. Adequate pain control requires thorough and precise assessment of the patient's pain history, patient's type and pattern of pain, including onset, location, intensity, and factors that ease or exacerbate the pain. Relevant psychosocial and ''quality-of-life'' factors may determine the patient's (and family's) ability to cope and should also be assessed before implantation [12, 23, 25, 26].

The conditions that may be causes of pain and represent indications for intrathecal drug-delivery systems include: failed back syndrome, neuropathic pain, axial spinal pain, complex regional pain syndrome, diffuse pain, brachial plexitis, central pain, failed SCS therapy, arachnoditis, poststroke pain, spinal cord injury pain, and painful peripheral neuropathy [10, 21, 30–32]. However, at present there is no way to predict the effect of intrathecal opioid application.

Surgical aspects

Before intrathecal catheter placement, the skin at the lower back including the midline and paramedian area is prepared with aseptic solution before local anaesthetics are injected. To avoid any damage to the conus medullaris, the puncture is performed at the L2/3 or L3/4 level with a Tuohy needle. The catheter is then inserted through the needle into the intrathecal space, the needle is withdrawn, and the catheter is advanced up to the desired level under fluoroscopic control. The target point for the catheter tip is around the level of the sixth thoracic vertebra (T6) in most cases, depending on the level

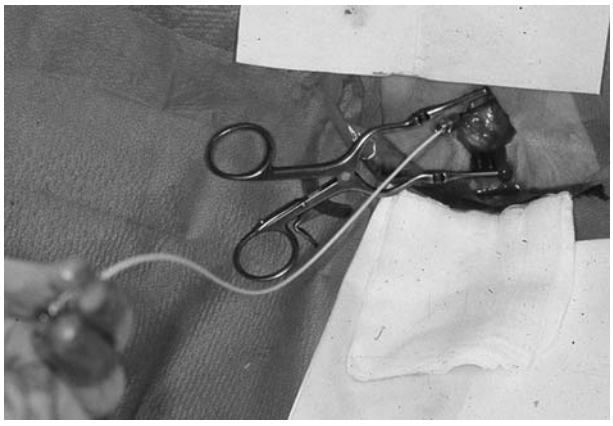

Fig. 1. Insertion of the catheter into the intrathecal space and connection to external pump

of the most intense pain. A subcutaneous tunnel is created with the point of catheter exit in some distance from the midline to prevent local infection and meningitis (Fig. 1). After insertion and tunneling of the catheter, an external programmable pump for continuous opioid application is connected. During a trial period of at least 7 days, patients report the effect of intrathecal therapy. During this period, the patient remains hospitalized and is investigated intensively on the basis of his pain diary. A pain reduction of >50% on the Visual Analogue Scale (VAS) is considered a good response to intrathecal drug application and a sufficient indication for the subcutaneous implantation of a pump for continuous drug application (Fig. 2). Modern implantable pumps such as the SynchroMed pump (Medtronic) are programmable,

Fig. 2. Example of an implantable pump (Codman) with sideport for intrathecal drug application

battery-powered devices that store and deliver medication according to instructions received from an external programmer [11, 14]. The main differences between the various pump models are the size of the reservoir and the presence of a side catheter access port.

Drug-related side effects can be divided into: a) dose-independent such as urinary retention, pruritus, pain related to bolus injection, perspiration, and sedation, and b) dose-dependent such as nausea, constipation, dysphoria, euphoria, sedation, respiratory depression, hypotension, central depression, and tachyphylaxis. Drug-withdrawal symptoms include anxiety, depression, and increased pain and may indicate mechanical problems, such as pump failure or catheter blockage and kinking.

Pharmacological aspects of intrathecal morphine application

It is assumed that the analgesic effect of opioids is mediated via conformation changes of selective receptors in the dorsal horn of the spinal cord and in relevant areas of the brain. After direct intrathecal application, very high concentrations of morphine can reach the receptor sites. Approximately 79% of morphine glucuronation is assumed to take place in the liver [24]. Recently, glucuronide formation was detected also in human brain tissue samples [29]. Because of the proximity to the opioid receptors, even minute amounts of metabolites may have significant pharmacological effects.

M6G is a potent u-opioid agonist and has been shown to be 13-fold more potent than morphine itself. It is suggested that up to 85% of the analgesic activity of morphine might be attributable to M6G. With respect to M3G, on the other hand, there is evidence from experimental animal studies that it may antagonize the analgesic effects of morphine and M6G [13, 17].

In 1996, we analyzed the concentrations of morphine (M) and its metabolites (M3G, M6G) in serum and spinal fluid of patients who received intrathecal morphine therapy in our department [17]. This intensified drug monitoring was repeated regularly when the pump was refilled. Concentrations could be compared to elucidate the distribution of the administered M and the production of its glucuronides. Determinations were performed in intervals of 1–3 months. CSF was obtained from the sideport of the pump. First, 1 ml representing the volume of sideport and catheter was aspirated followed by two samples of 2 ml CSF each. During the same session, a sample of venous blood was taken; plasma was separated and stored at $-20\,^{\circ}C$ together with the CSF sample. Using high performance liquid chromatography (PLC)-method as described by Stevenson *et al.* in 1982, the concentrations of morphine, M3G and M6G in serum and CSF were analyzed. The applied therapeutic dose of M varied from 3–45 mg/d depending on the needs of each individual patient. Pain relief of more than 50% was achieved in 80% of patients. M serum concentrations were significantly lower (<0.035 mg/l) than M concentrations in CSF (11–176 mg/l). M6G and M3G concentrations in CSF were very low (<84 μg). M6G and M3G concentrations in the serum were much higher than the M serum concentration (Fig. 3).

In one patient, we performed a lumbar puncture (L4–L5 level) after one CSF sample was obtained from the sideport of the pump. The concentrations of CSF morphine from the sideport (catheter tip at T5 level) and CSF M from the lumbar puncture were compared. In this case, M concentration at T5 was 34.5 mg/l and at L4–L5 level was 8.7 m, a difference suggestive of local diffusion difficulties within the CSF spinal subarachnoid space.

This study showed that in CSF, M concentration was about three thousand times higher than the concentration of M6G and M3G. On the basis of this data, we conclude that the main analgesic effect of intrathecal application can be attributed to M ''itself''.

Most of M3G and M6G in CSF probably reflect hepatic transformation of free M in the plasma. The metabolites probably reach the intrathecal space via backward-diffusion since the serum concentrations of the metabolites exceed the CSF concentrations by about 6 times. We have to keep in mind the larger size and lower lipid solubility of the metabolites, which make their passage into CSF more difficult. Following oral application, mean CSF concentration of M is only about 16% of the concentration in serum [33]. In our intrathecal series the mean serum/CSF concentration ratio for M is 1/3000; this probably explains the much lower rate of systemic side effects. We assume that local diffusion difficulties cause an uneven distribution of M in CSF. Therefore, the clinical effect is markedly influenced by the position of the catheter tip; one should be aware of this during catheter implantation.

Results of long-term intrathecal opioid application for intractable pain: the Cologne experience

In the Department of Stereotaxy and Functional Neurosurgery of Cologne University, 322 patients received an implantable pump from 1998 to 1995. Of these patients, 101 suffered from cancer pain, and 221 from chronic, non-malignant pain syndromes (116 neuropathic, 54

deafferentiation, 51 nociceptive pain). We analyzed the long-term results after more than 3 years in 101 of these patients. In 72 patients (71.3)%, the reduction of pain as assessed with the VAS was >50% i.e. good or excellent. In 20 patients (19.8%), the results were fair (VAS 5–6) and in 9 (8.9%), the long-term results after 3 years of

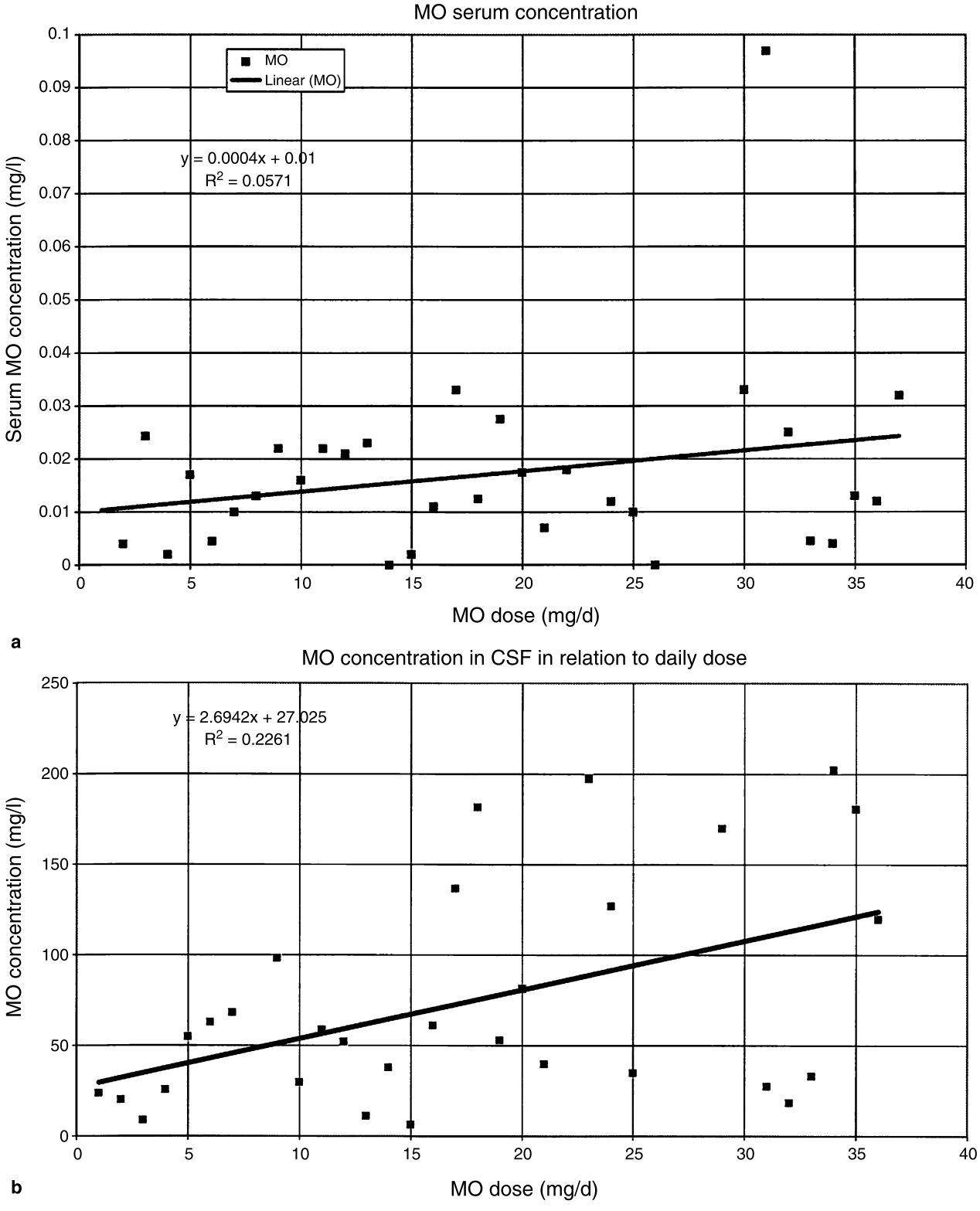

Fig. 3. (a) Morphine serum concentration in relationship to daily dose (mg/l), (b) morphine CSF concentration in relationship to daily dose (mg/l), (c) concentrations of morphine and its metabolites in CSF and serum (mg/l)

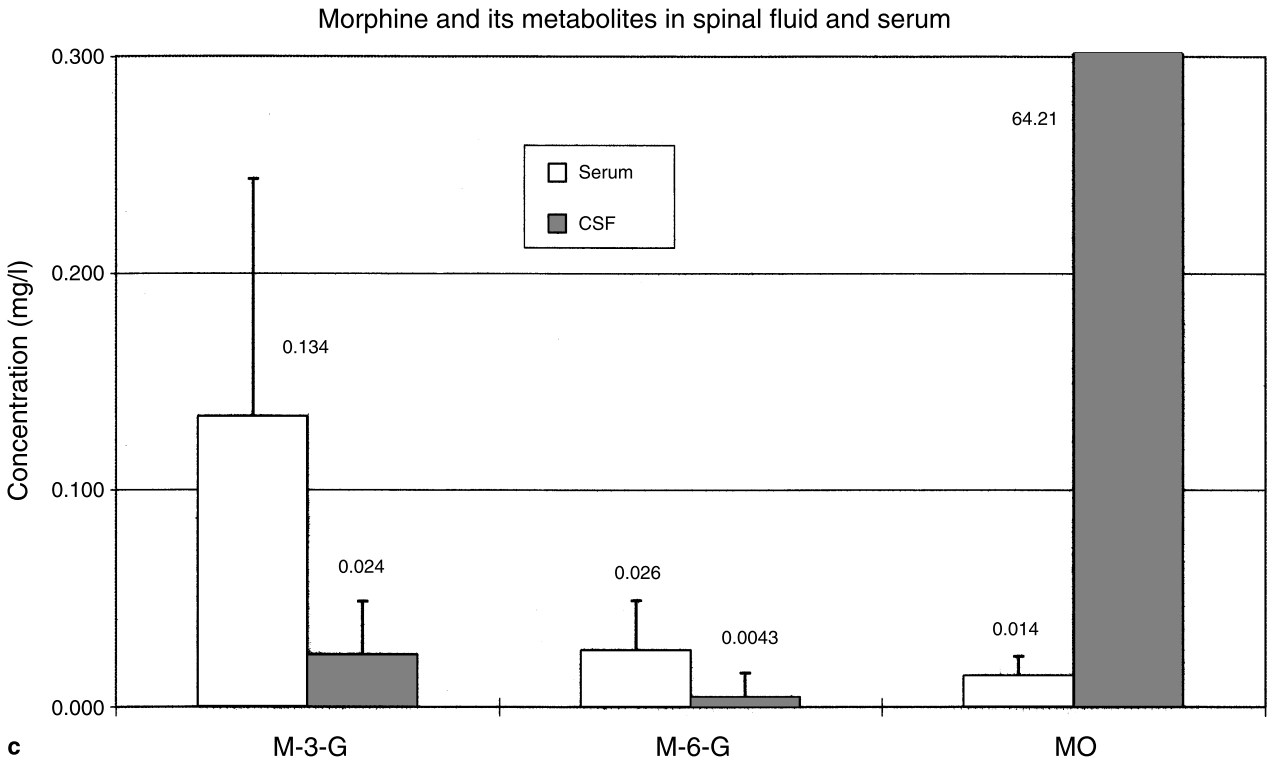

Fig. 3 (*continued*)

continuous intrathecal opioid application were poor (VAS: 7–10).

Over a period of 8 years, we also looked at side effects and complications of long-term intrathecal opioid application with implantable pumps. We observed catheter-related technical problems such as catheter dislocation, obstruction, kinking, disconnection or rupture in 17 of 165 patients. Pump malfunctions were very rare (8 of 165 cases) and limited to older pump types. Rotation of the pump occurred only in one patient who was very obese. Refilling of the pump was not possible in this patient which required re-operation for subcutaneous fixation of the pump. Similar to other operations, we also observed general non-specific surgical complications. Wound healing impairment occurred in 8 (4.8%) and subcutaneous pocket fluid collections in 8 patients (4.8%); the subcutaneous fluid was seroma in 5 and hematoma in 3 patients. These complications were managed easily after a single puncture in most cases. In 3 patients (1.8%) a more severe local complication occurred i.e. a cutaneous perforation of the pump. This was managed by removal of the pump and antibiotic therapy. CSF fistulas occurred in 2 (1.1%) and meningitis in 2 patients (1.1%). All these complications were reversible, leaving no permanent damage.

The following drug-related side effects of long-term therapy with intrathecal pumps were described by 32 of 165 patients: slight somnolence 3 (1.2%), urinary retention 2 (1.21%), constipation 8 (4.84%), nausea 2 (1.21%), vomiting 1 (0.60%), pruritus 3 (1.18%), sweating 3 (1.18%), edema 6 (3.63%), nightmares 1 (0.6%), and hypotension 2 patients (1.21%). Hence, the overall rate of medical complications in long-term therapy with intrathecal pumps during 8 years of follow up was 13.9%.

Intrathecal combination therapy

Intrathecal monotherapy is successful in most patients with chronic intractable pain syndromes. However, in about 30% of patients, no satisfactory reduction of pain is achieved. We introduced intrathecal combination therapy with morphine and baclofen in patients with burning, cramp-like pain and associated spasticity and dystonia.

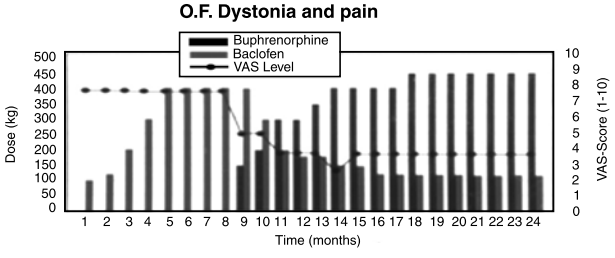

Fig. 4. VAS score over 2 years in a patient with severe pain and dystonia. After 9 months of intrathecal monotherapy with baclofen, intrathecal combination therapy was commenced with addition of buprenorphine

Combination with other drugs is also possible (Fig. 4). Clonidin as well as local anaesthetic drugs have been used either as sole treatment or in combination with opioids (morphine, methadone, polamidone, buphrenorphine). The underlying pathology included lumbar arachnoiditis, multiple sclerosis, cerebral apoplexy, root avulsions and tumors. In our series (follow-up: 2–36 months), 60% of the patients who did not respond to intrathecal monotherapy, reported a significantly lower VAS pain score with intrathecal combination therapy. Side effects were rare, reversible, and comparable to those of intrathecal monotherapy in frequency and severity. The experience obtained in these cases indicates that, in carefully selected patients who do not benefit from intrathecal monotherapy, pain can be managed satisfactorily with morphine/baclofen combination therapy [15].

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Management of chronic back and leg pain by intrathecal drug delivery

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Summary

Intrathecal delivery of analgesic drugs by implantable pump systems has been recognized as a treatment option for patients with chronic pain of benign or malignant origin that is resistant to oral or parenteral medication. Patients with chronic back and leg pain (CBLP), a benign but severely disabling condition of the lumbar spine with multifactorial genesis, have been demonstrated in a number of retrospective and in some prospective clinical studies to benefit from intrathecal delivery of opioid and/or non-opioid substances, either as single drugs or in combinations. In addition, intrathecal therapy for CBLP has been proven safe and less expensive that conventional medical therapy.

This chapter summarizes the clinical and experimental evidence and the personal experience of the authors with long-term intrathecal infusion therapy for CBLP. It discusses important clinical issues such as drug selection, drug combinations, and side effects and complications of intrathecal infusion. It is concluded that further clinical research is needed in order to provide stronger evidence for the usefulness of a number of drugs currently used for intrathecal therapy on a mostly empirical basis.

Keywords: Bupivacaine; chronic back and leg pain; CBLP; intrathecal infusion; implantable pump; morphine.

Introduction

Intrathecal infusion of drugs by implantable subcutaneous devices has been recognized as a viable alternative option for the treatment of patients with chronic pain resistant to oral or parenteral analgesics [12, 21, 34]. There are currently three major classes of agents used in the management of chronic pain by intrathecal infusion: opioids, local anesthetics, and non-opioids such as adrenergic receptor agonists or NMDA receptor antagonists. Opioids are the first choice for intrathecal infusion, with morphine being the most frequently used drug and the only one approved for intrathecal use by the US Food and Drug Administration [11]. There is extensive clinical experience with intrathecal morphine not only in patients with chronic pain of benign origin, but also in cases with malignant (cancer-associated) pain [22, 34]. Its efficacy and side effects are well known. Other opioids such as hydromorphone are less well investigated, but are increasingly chosen because of some advantages over morphine [19].

Patients with chronic back and leg pain (CBLP) due to degenerative spinal disease and spinal surgery are a challenge to every pain clinician because of the disabling nature of the disease and its resistance to medical therapy [20, 24]. CBLP is a benign condition and therefore the clinical history of some patients may be rather lengthy. CBLP patients require systematic long-term follow-up and regular medical assessments because the severity of their condition may vary considerably over time. Intrathecal opioids show good analgesic efficacy in these patients, however tolerance development and neuropathic pain components may require additional non-opioid drugs administered intrathecally in combination with opioids [25, 27].

This review summarizes significant clinical and experimental evidence on long-term intrathecal infusion therapy of patients with CBLP. It discusses important practical issues such as selection and effects of analgesic drugs and their combinations, side effects and complications of intrathecal drug infusion, and outlines future developments in the field.

Chronic back and leg pain (CBLP) syndrome

CBLP is a complex chronic pain syndrome also known as failed back surgery syndrome and commonly defined by its anatomical localization and duration [20, 31]. It is of multifactorial genesis and may be the consequence of various lumbar spinal diseases, including arachnoiditis,

degenerative disc disease, epidural fibrosis, lumbar disc herniation, osteoporosis, or spinal canal stenosis [24, 33]. Pain patterns in CBLP may include neuropathic components, but the main feature is usually nociceptive pain.

CBLP is not a very common pain condition. Only 5% of patients suffering with acute back pain and leg pain (sciatica) will subsequently develop CBLP, however it is currently not possible to predict which acute cases will evolve into chronic pain sufferers [31, 33]. Although degenerative or postsurgical disc pathology is thought to be a common cause of CBLP, the relationship between the extent of disc damage and the degree of clinical symptoms is not clear [20]. A strictly mechanical or pathoanatomical explanation for CBLP has proved inadequate.

Transition from acute to chronic pain is also influenced by psychological factors, which include behavioral, cognitive-affective, and psycho-physiological mechanisms [20, 31, 33]. Psycho-physiological mechanisms are triggered by organic injury or spontaneous degeneration and may lead to generalized muscle overactivity, increased fatigue, and other pain problems such as tension myalgia and headache. The emotional stress produced by chronic pain tends to stimulate the activity of the sympathetic nervous system, which may further amplify nociception through peripheral or central mechanisms [20].

Selection of drugs for intrathecal therapy of chronic pain

The efficacy of intrathecal delivery of opioids has been demonstrated both in patients with pain related to cancer or to CBLP and other non-malignant conditions [21–23, 34]. Initially, intrathecal long-term delivery of morphine in patients with chronic pain of benign origin was viewed somewhat controversially due to concerns about the development of opioid tolerance, abuse, and addiction [15]. However, clinical studies have clearly demonstrated a very low incidence of opioid addiction and a low rate of side effects [25, 26].

The use of programmable electronic pumps may have some advantages over the less expensive non-programmable (constant-flow) mechanical devices [28]. In a study of patients with chronic pain due to non-malignant conditions, delivery of morphine through an implanted programmable pump provided good to excellent pain relief for the majority of patients [14]. The pump was programmed to deliver morphine in a variety of patterns to match each patient's individual analgesic needs. In a retrospective multicenter study of 429 patients with pain due to either cancer or non-malignant disease, it was suggested that the use of programmable pumps for delivery of intrathecal morphine provided pain relief in the majority of patients [21]. The mean percentage of pain relief was 61% for all patients, and more than 95% experienced excellent or good pain relief.

An interdisciplinary expert panel carried out a large internet-based survey and systematically reviewed the literature in order to propose a scheme for the selection of drugs for intrathecal infusion therapy [3]. It was universally accepted that the approach to intraspinal infusion should be viewed as a hierarchy of therapeutic strategies – first-line to fourth-line approaches, based both on the availability of published data from clinical studies and on the use of the respective drug in routine clinical practice.

It was agreed that morphine should be considered first-line strategy for most patients with chronic pain. Although large randomized trials are still lacking, the use of morphine is nevertheless supported by a relatively large body of published literature and by a long history of clinical use [3]. If intrathecal infusion of morphine alone provides insufficient analgesia, a few second-line strategies may be considered, mostly the combination of morphine with a local anesthetic (bupivacaine) or with an adrenergic receptor agonist (clonidine), or the use of an alternative opioid such as hydromorphone. Combinations of morphine with bupivacaine or with clonidine could be considered when the pain syndrome has a neuropathic component. Literature on second-line approaches is however limited and there is no systematic information to support the preferential use of one combination over another. When second-line options do not provide adequate pain relief, third-line approaches may be considered. Such are the combination of morphine, bupivacaine, and clonidine, or an alternative opioid, specifically fentanyl or sufentanil, or the combination of hydromorphone with bupivacaine or clonidine. Data supporting these combinations are very limited and clinical use is infrequent. Finally, forth-line approaches may be considered in the uncommon case of failure of all previous options and strategies. These are supported solely by preclinical data and by anecdotal clinical cases. Forth-line approaches are the use of intrathecal drugs such as the opioids meperidine or methadone, the neuroleptic droperidol, the NMDA receptors antagonists ketamine or memantine, or the γ-amino-butyric acid (GABA) agonists midazolam or baclofen. It is recommended that the use of these drugs is limited to appropriate clinical research protocols [3].

In 2003, the above recommendations were updated and modified to accommodate the rapid changes that have occurred in the last few years in the area of intrathecal drug delivery [11]. Although the hierarchical structure of the treatment approaches was not significantly modified, recommendations for the use of some drugs changed. In addition, new requirements were formulated such as the amount of minimum evidence necessary to support the use of a drug for intraspinal infusion [11]. According to these most recent recommendations, first-line therapy consists of morphine and of hydromorphone. Second-line therapy includes morphine or hydromorphone combined with either bupivacaine or clonidine. If any of these combinations results in inadequate analgesia or intolerable side effects, a change to an alternative second-line combination or to third-line drugs is recommended. As a third-line approach, both bupivacaine and clonidine may be added to either morphine or hydromorphone. Forth-line drugs include the lipophilic opioids fentanyl and sufentanil, and the GABA agonists midazolam and baclofen [11].

Evidence of efficacy of intrathecal therapy for chronic pain

Opioids

Randomized and controlled prospective clinical trials investigating intrathecal morphine for chronic pain are lacking. There are however a few prospective multicenter studies, and numerous retrospective studies and case reports (for review see Ref. [4]).

A prospective long-term survey of 16 patients reported that intrathecal morphine reduced pain scores for all types of pain, with the greatest efficacy found somewhat surprisingly in patients with neuropathic and mixed (neuropathic/nociceptive) pain [17]. A prospective study within the framework of the National Outcomes Registry for Low Back Pain collected data on 136 patients with chronic low back pain treated with intrathecal infusion via implantable pumps. Of these 136 patients, 81% received morphine. Oswestry scale ratings improved after 1 year by 47% in patients with back pain, and by 31% in patients with leg pain [7]. Thimineur *et al.* carried out a prospective study of long-term outcome from intrathecal morphine therapy in chronic pain of benign origin [32]. The study included two comparative groups – 38 cases with implanted pumps and 31 cases without implanted pumps. Results suggested that severe chronic pain patients do benefit from intrathecal therapy, but the overall severity of pain and symptoms still remains high. Anderson and Burchiel [1] treated 30 patients with benign chronic pain with intrathecal morphine infusions and managed insufficient analgesia by addition of bupivacaine in over 20% of all patients. These authors did not see any major side effects specifically related to bupivacaine use. They described tolerance development to morphine with an increase from 2 mg/24 h at baseline to 14.5 mg/24 h at 24 months, and a median plateau type dose progression curve previously known from other opioid studies [2]. Roberts *et al.* investigated 88 patients with chronic pain of benign origin treated with long-term intrathecal opioid infusion (average duration >36 months) [29]. Mean pain relief was 60%, and 74% of patients reported increased activity levels with therapy. Doses of oral medication were significantly reduced. Opioid side effects included endocrinological disturbances and spinal and supraspinal symptoms. Hardware complications required at least one further surgical procedure in 40% of the patients. The mean intrathecal morphine dose increased by more than 60% over 36 months [29]. Further studies reported similar figures for efficacy and complication rates [21–23, 34].

Intrathecal hydromorphone is increasingly used by pain clinicians in recent years [11]. The potency of hydromorphone is about 5 times that of morphine, but the side effect profile is equivalent or better than that of morphine [19]. As an additional practical benefit, the use of hydromorphone allows longer periods of time between pump refills. Few studies of intrathecal hydromorphone for chronic pain have been performed, and there have been no controlled trials.

Local anesthetics

Bupivacaine as monotherapy or in combination with opioids was demonstrated to be well suitable for the treatment of chronic pain and free of significant side effects [23]. In a randomized, double-blind, multiple-phase crossover trial of 24 patients with chronic non-malignant pain, the addition of bupivacaine to morphine or hydromorphone produced a statistically significant improvement in quality-of-life (QOL) scores. However, neither a dose-related response nor a significant effect on pain scores was observed [18]. In a prospective study of 47 non-cancer patients, Anderson and Burchiel observed a 50% response rate 2 years after start of intrathecal opioids in combination with bupivacaine [1]. Retrospective analysis confirmed the lack of significant side-effects

due to intrathecal bupivacaine. Deer *et al.* examined a large patient group ($n = 109$) consisting of patients with CBLP ($n = 84$) or with pain of malignant origin who received bupivacaine in combination with opioids over an extended period of time [8]. The findings suggested that addition of bupivacaine to opioids significantly improved pain relief and patient satisfaction and significantly reduced doses of oral analgesics. The total dose of morphine was reduced by 23% in the combination group compared to the morphine only group. No major adverse effects and no new neurologic deficits were reported in patients exposed to opioid-bupivacaine combinations [8].

Adrenergic agonists

The selective α_2-adrenergic agonist clonidine, a lipophilic drug with rapid onset and short duration of action, inhibits nociceptive impulses by activating adrenoreceptors in the dorsal horn of the spinal cord [19]. A synergism is proposed between clonidine and opioids. Predominant side effects reported for intrathecal clonidine are dose-dependent bradycardia and blood pressure changes [23].

Hassenbusch *et al.* reported a prospective study of 31 patients (25 with non-malignant pain) who received intrathecal clonidine as a single analgesic drug [10]. Twenty-two patients progressed through the dose-escalation stage and achieved >50% pain or symptom reduction without intolerable side effects. At 6 months, 77% of them achieved good pain relief and 59% were considered long-term successes. No tolerance development to clonidine was observed over time [10].

Other agents

Spinal NMDA receptors play an important role in the processing of pain resulting from tissue and nerve injury and in the development of tolerance. NMDA receptor antagonists however lack a significant safety record for intrathecal infusion. Moreover, redistribution of these agents in different spinal compartments may result in supraspinal side effects such as hypotension [10, 19]. Published data on the intrathecal delivery of NMDA receptor antagonists is limited to ketamine. Midazolam is a benzodiazepine class drug acting on the benzodiazepine/$GABA_A$ receptor complex. Midazolam has been used intrathecally in animal experiments and proven to produce analgesia in acute pain models. Intrathecal bolus doses of midazolam have been used and demonstrated to result in segmental analgesia with long-term effects after one-time application [30]. Early clinical studies have been conducted in acute and chronic pain conditions and have proved analgesic efficacy of epidural or intrathecal midazolam as a single drug or in combination with opioids or local anesthetics [2, 28, 30].

Personal experience with intrathecal infusion of drug combinations for CBLP

Although morphine currently represents the gold standard for intrathecal analgesia by infusion of a single drug, other opioids such as hydromorphone, fentanyl, sufentanil, and meperidine are now being successfully used in patients who do not tolerate morphine. While these opioids have shown sufficient efficacy against nociceptive pain, analgesia in neuropathic or peripheral-neuropathic pain is often incomplete, and addition of bupivacaine or clonidine is necessary [11, 19].

Our personal experience with intrathecal morphine in patients with CBLP who are resistant to medical therapy and to high-dose oral or parenteral opioids demonstrates a rather limited long-term success. In the majority of cases, the dose of morphine dose has to be increased rapidly, often reaching the 10-fold of the initial dose within a year. Despite relatively high doses of morphine, we are sometimes unable to achieve sufficient relief of the often present neuropathic and/or peripheral-neuropathic type of pain. On the other hand, most patients on a high dose of intrathecal morphine complain of side effects, such as nausea, sedation, profuse sweating, and severe constipation. To circumvent these shortcomings of intrathecal infusion therapy for CBLP, we designed and systematically tested a stepwise polyanalgesia approach in these patients [28]. An open prospective study included 26 patients (15 females and 11 males) with a median age of 54 years (range 35–68 years). Only patients were enrolled who underwent at least one spinal surgery procedure for lumbar disc herniation or lumbar spinal stenosis, with or without instrumented fusion, and who had developed postoperatively CBLP refractory to standard medical treatment according to the WHO pain treatment ladder. Pain was diagnosed as mixed neuropathic/nociceptive in 18 of 26 patients (69%), radicular neuropathic with a minor nociceptive component in 6 cases (23%), and mixed radicular/peripheral neuropathic in 2 patients (8%). Pain area patterns in all patients included axial low back pain and unilateral or bilateral buttock and leg pain of irregular pattern (not confined to anatomically defined dermatomes). For patients

with mixed neuropathic-nociceptive pain, trial infusions were started with morphine and clonidine. Patients with predominantly neuropathic or radicular/peripheral neuropathic pain were treated with morphine, clonidine and/or bupivacaine. If the pain was not sufficiently reduced with this medication, midazolam was added to the infusate. A portable external pump was used for all test infusions (Fresenius GmbH, Berlin, Germany), and a volume of 2 ml/24 h was infused intrathecally. Typically, test infusion was started with 0.5 mg/24 h morphine and titration was performed until a pain response was noted. Clonidine was added at 0.015 mg/24 h, and bupivacaine at 0.5 mg/24 h. Midazolam starting dose was 0.2 mg/24 h. The amount of pain reduction during the trial period varied in each patient, and was optimized on a case-by-case basis primarily by titration of morphine. If the starting dose of morphine had to be doubled during titration, the adjuvant drugs were titrated one by one to improve analgesic effects at the same opioid dose. Only after doubling the doses of adjuvant drugs was morphine dose increased further. After reaching and maintaining sufficient analgesia (at least 50% reduction in intensity and unpleasantness of all pain components, as well as subjective satisfaction of the patient), a SynchroMed® programmable pump (Medtronic, Inc., Minneapolis, MN) was permanently implanted and filled with the best performing combination of drugs at the concentrations used during the trial period. Patients were followed monthly for the first 3 months after pump implantation, then every 3 months. Long-term treatment efficacy was defined by patient-reported reduction of pain and additional analgesic medication and by functional improvement and subjective satisfaction.

Mean follow-up time after implantation was 27 ± 11 months (mean $\pm$ SD). During follow up, analgesic effects of intrathecal drug infusion varied somewhat, but remained constantly under the 50% mark compared to the initial pre-implantation findings. Morphine doses had to be increased over time, but the dose increase was rather moderate. It was noted that pain also changed with time of infusion, and some patients reported on newly occurred neuropathic or nociceptive pain components, which were then treated by adding to the pump the respective drug not given to the patient up to that point (e.g. midazolam if the patient was treated previously by morphine/clonidine/bupivacaine, or bupivacaine if the patient was treated by morphine/clonidine/midazolam). Two years after pump implantation, intrathecal morphine was administered to a total of 26 patients (100%), bupivacaine to 20 (77%), clonidine to 16 (62%), and midazolam to 10 (38%).

No major clinical side effects of the treatment, such as myelopathy, permanent loss of bladder control, or motor weakness, were encountered, besides the usual mild temporary side effects of morphine (constipation, nausea, pruritus, hesitant micturition). Besides the assessment of pain severity, permanent neurological signs and symptoms were evaluated 2 years after start of intrathecal drug infusion. The greatest benefits were seen in ambulation, both improved walking ability and prolonged walking distance, as well as in the nearly complete reduction of supplemental oral or parenteral analgesics. There was also an improvement in sleep and sensomotor disturbances. Seventy-three percent ($n = 19$) of the patients rated the long term treatment result as excellent or good, 23% ($n = 6$) as sufficient, and only 1 patient (4%) described poor results. Hardware complications were a rare event in our CBLP patients. In 2 cases (8%), there was a catheter leakage or occlusion 4 and 9 months post-implant, respectively, which was noted because of rapid decline in analgesic efficacy despite repeated dose increases and pump refills. After catheter replacement, effective analgesia was restored. In one patient, the reservoir septum became leaky after 14 months of usage, and the pump had to be replaced. No serious catheter or pump infections leading to removal of the implant were noted [28].

Complications and side effects of clinically relevant drugs

Stability of intrathecal drugs and their combinations over time is a concern with implantable delivery systems. Wulf *et al.* investigated stability of morphine, clonidine and bupivacaine during up to 90 days, and found no macroscopic or microbiological signs of precipitation, change in color, contamination, or pH shift. None of these three drugs declined in concentration during the observation period [35].

Formation of an inflammatory mass (granuloma) at the tip of the intrathecal catheter has been recognized as a serious complication of long-term intrathecal delivery of opioids [9]. Coffey and Burchiel analyzed reports of catheter tip granulomas in 39 patients who received intrathecal morphine or hydromorphone, either alone or mixed with other drugs, and noted that the presence of a granuloma was invariably related to administration of intrathecal opioids [5]. The authors recommended minimizing opioid dosage and concentration and providing

close follow-up of patients to reduce the risk of neurological injury. Further reports confirmed that catheter tip granuloma appears to increase with concentration and dose of the opioids [9]. It was recommended that, if possible, morphine should be infused at a maximum concentration of 30 mg/ml and a maximum dosage of 15 mg/day. Animal data suggest a lower risk of granuloma formation from hydromorphone than from morphine [36]. Further opioid-related side effects are related to the hypothalamic-pituitary function [29]. Patients treated with intrathecal morphine show reduced levels of gonadotropic hormones, growth hormone, and cortisol, and some of them may benefit from hormone replacement therapy [25].

Intrathecal bupivacaine is remarkably well tolerated. It is recommended that bupivacaine doses do not exceed 30 mg/day at a maximum concentration of 38 mg/ml (3.8%). This total daily dosage is likely to preserve lower extremity and bladder function in most patients, although in some cases it has been shown to produce sympathetic blockade, somatosensory blockade, and/or motor blockade [13].

Based on extensive clinical experience and on the lack of observed neurotoxicity, a dosage range of 10–1000 μg/day is recommended for clonidine, although the risk for significant side effects seems higher in the upper part of this range. Side effects may include hypotension, sedation, peripheral edema, and cardiac arrhythmias [10].

Economic aspects of long-term intrathecal therapy for chronic nonmalignant pain

De Lissovoy *et al.* conducted a computer simulation study of outcomes in patients with failed back surgery. The objective was to estimate the direct cost of intrathecal morphine therapy delivered via an implantable pump compared to alternative therapy (medical management) over a 5-year course of treatment. Results from this computer simulation indicated that long term intrathecal infusion of morphine appears to be cost-effective when compared with alternative (medical) management when the duration of therapy exceeds 12 months [6]. Kumar *et al.* compared in a prospective clinical study the cost-effectiveness of intrathecal drug therapy with that of conventional pain therapy in patients suffering from CBLP. From 67 patients with chronic pain related to failed back surgery syndrome, 23 underwent implantation of a programmable pump and 44 were treated with conventional pain therapy and acted as controls. Patients were followed for a 5-year period and the impact of treatment on the quality of life was also assessed. The actual cumulative costs for intrathecal therapy during a 5-year period was more than 30% higher than that for conventional pain therapy. High initial costs of hardware were however recovered by 28 months. After this time point, managing patients with conventional therapy became the more expensive treatment option for the remainder of the follow-up period [16].

Obviously, considerable differences in the medical care systems of different countries make meaningful international comparisons almost impossible, but nationwide surveys consistently confirm the notion that, above and beyond its superior analgesic efficacy in selected cases, long-term intrathecal drug therapy is more economical than medical pain therapy, with a country- and health care system-specific break-even period of varying duration.

Conclusions

Advances in pain research and pain therapy were combined with quantum leaps in the development of new implantable technologies to develop long-term intrathecal therapy as a safe and efficacious routine clinical approach to chronic pain resistant to oral or parenteral medication. Unfortunately, clinical capabilities for safe drug delivery have advanced rapidly beyond the scientific foundation of these approaches. Studies in the field have been mostly retrospective, and considerable variations between study designs have made useful comparisons of existing data very difficult [4]. Clinical efficacy of intrathecal drug delivery remains to be demonstrated in prospective large-scale randomized and controlled trials. Currently there is also little information about long-term efficacy and safety of the numerous drugs that have been used intraspinally in second, third and forth-line approaches [3, 11]. Important information about pump-drug compatibility, drug-drug stability, and the effects of the pH on outcome is lacking [35]. Clearly, further research in the intrathecal delivery of pain medications is warranted and needed if a more widespread and evidence-based acceptance of this strategy is to be achieved. Currently it seems however accepted among pain clinicians that the clinical use of intrathecal drugs has less rigid aims, criteria, and endpoints than academic research studies, although the gap between these two areas need to be reduced and eventually closed [11].

Based on extensive clinical experience and review of the current literature, intrathecal morphine appears to be

safe at moderate clinical concentrations and has favorable efficacy data. Limited information on other opioids also appears favorable from both a toxicology and efficacy standpoint [4, 19, 23]. Bupivacaine is the only local anesthetic agent that currently shows favorable data for both clinical efficacy and toxicology [11]. Based on the currently available literature, both clinical efficacy and toxicology for clonidine appear encouraging [10]. Combinations of different drug classes such as opioids with local anesthetics, opioids with clonidine, and opioids with local anesthetics and/or clonidine are currently being used in clinical practice without hard evidence for synergism [3, 45]. The efficacy reports appear favorable, but are based largely on case studies and retrospective analysis. Little information is available on the long-term compatibility of these combinations [11, 19]. Clinical and laboratory research on gabapentin, NMDA antagonists, naloxone, calcium channel blockers, midazolam, and cyclooxygenase-2 inhibitors is currently being carried out and may eventually lead to the discovery of additional clinically relevant treatment modalities [11]. Finally, further research is needed to select the best clinical applications for many of the compounds currently used in clinical practice without well defined indications.

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Drug-enhanced spinal stimulation for pain: a new strategy

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Summary

Neuropathic pain is notoriously difficult to manage and only a few classes of drugs may provide adequate benefits. Thus, in many cases spinal cord stimulation (SCS) is considered; however, in this group of patients, between 30–50% of the cases offered a percutaneous SCS trial may fail to obtain a satisfactory effect. Additionally, a certain number of patients with a good initial effect, report that after a period the benefits are reduced necessitating additional peroral drug therapy.

Based on animal studies of transmitters and receptors involved in the effects of SCS in neuropathic pain, the GABA-B receptor seems to play a pivotal role for the effect and, moreover, the agonist baclofen injected intrathecally in rats potentiated the SCS effect in animals not responsive to SCS per se. Based on these and further studies, 48 patients with neuropathic pain and inadequate response to SCS were given intrathecal (i.t.) baclofen (ITB) in bolus doses as an adjuvant.

In this group 7 patients enjoyed such a good effect that they were implanted with both SCS and drug delivery systems for ITB. Four additional cases received baclofen pumps alone. Some other patients were given intrathecal (i.t.) adenosine in combination with SCS and initially preferred this to baclofen. The chronic use of this drug in a pump however proved to be technically problematic and all the adenosine cases were eventually terminated.

At follow-ups, in average 32 and 67 months after start of SCS + baclofen therapy, more than 50% still enjoy a very good effect. The daily dose of baclofen needed to maintain the effects was approximately doubled during the observation period. There were few and mild side-effects. However, in a group of three patients with peroral baclofen therapy and SCS, complaints of side-effects were common and this therapy was terminated. Informal reports from collegues support the negative experience with additional peroral baclofen.

In conclusion, in patients with neuropathic pain demonstrating inadequate response to SCS (small VAS reduction; short duration) a trial of intrathecal baclofen in combination with SCS may be warranted.

Keywords: Neuropathic pain; spinal cord stimulation; baclofen; adenosine; clonidine; gabapentin; pregabalin; rat; human trials.

Introduction

Spinal cord stimulation (SCS) is a minimally invasive, reversible, and in well selected cases, very cost-efficient therapy for chronic pain resistant to pharmacological regimens [17, 26, 33] (c.f. also other chapters in this volume). However, in spite of very satisfactory results in some pain syndromes e.g. angina pectoris and vasospastic ischemic pain, many cases of neuropathic pain still pose a challenge to the clinician [26]. Even in groups of well-selected patients with chronic neuropathic pain, up to 30–50% do not experience sufficient pain alleviation during a one to two week percutaneous test with SCS and thus will not proceed to a full implant. There is as well a large group of patients in whom, after a period with satisfactory pain relief extending from about six months to more than 1 year, the effect of the stimulation diminishes and becomes inadequate, requiring additional peroral drug treatment; this previously, in most of the cases has been proven insufficient and carrying side-effects (e.g. tricyclic antidepressants and anticonvulsive compounds). Since SCS is often considered the last resource in many of these refractory pain conditions, the lack of effect – or loss of previous effect – in these patients poses a challenge to develop new therapeutic strategies.

The combination of SCS and drugs for treating such difficult pain syndromes is mainly based on the concept of enhancing or potentiating the effect of SCS by low doses of drugs where significant side effects are avoided. These drugs may act targeting the same specific receptor populations as SCS does, or by recruiting additional mechanisms of pain suppression, thereby providing a net reduction in pain levels.

There have been many attempts to predict the outcome of CNS stimulation through various pharmacological tests but so far none has proven efficient [29].

During the late seventies and early eighties experimental research on SCS mechanisms utilizing mainly neurophysiological approaches provided evidence for the recruitment of large diameter fiber systems in the spinal cord, activating ''the Gate Mechanism'' and inducing

changes also at the thalamic level [10, 18, 23, 28, 30, 32]. During the last two decades interest has been directed onto the neurochemical mechanisms involved in the beneficial effects of SCS and more specifically on transmitters and receptor subgroups [3, 28]. Based on such data from animal experiments, trials with tailored drug-enhanced SCS could be performed providing the foundation for clinical trials on patients.

Experimental foundations

The experimental background to the strategy presented in this chapter is based largely on studies of various types of animal models of neuropathic "pain-related behaviour" such as pathological withdrawal thresholds to innocuous tactile and thermic stimuli – reactions mimicking the allodynia observed in patients with peripheral nerve lesions [13].

Early animal experiments performed on normal healthy animals demonstrated release of transmitters supposed to be involved in suppression of nociception [24, 27]; these must be confirmed on animal models of neuropathic pain since nerve lesion have been demonstrated to markedly alter the transmitter concentration in the dorsal root ganglia and in the dorsal horns [15], possibly also altering the role of the transmitters.

During the last decade data has been accumulated regarding the central transmittor systems and receptors involved in the beneficial effects of SCS. For example, it was demonstrated a couple of years ago, that SCS induce the release of the inhibitory amino-acid GABA in the spinal dorsal horn in normal rats [27]; subsequently, in animal models of neuropathy [38], a clear relationship between the SCS-induced GABA release and the alleviation of the neuropathic symptom studied was also established (tactile hypersensitivity to touch in a nerve lesioned hind paw: "allodynia"). In a further study, it was observed that the beneficial effects of SCS, in the nerve-injured animals, were abolished if a GABA-B receptor antagonist was administered either intrathecally via an implanted catheter or via a microdialysis probe in a terminal acute experiment [4, 6]. On the contrary, intrathecal administration of the GABA-B receptor agonist baclofen in a very low, and per se ineffective, dose enhanced the effect and could convert non-SCS responding animals into good responders [4] (Fig. 1). A similar enhancing effect at even a very low dose of a drug administered intrathecally in experimental animals was established also for R-PIA, a compound acting on the adenosin A1-receptor [5, 7], and later for other pharma-

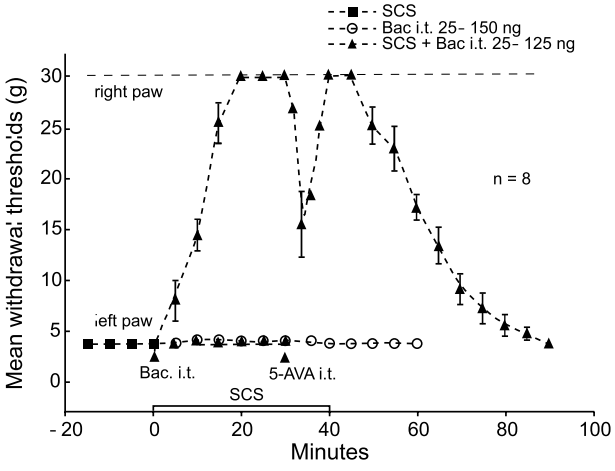

Fig. 1. The selected i.t. baclofen doses had no effect on withdrawal thresholds in the allodynic SCS non-responding rats, but in combination with SCS produced a normalization of the low withdrawal thresholds. At the end of the SCS, a GABA-B antagonist 5-AVA was i.t. administered resulting in an instantaneous and short-lasting drop of the thresholds values. [4] (*Reprinted with permission*)

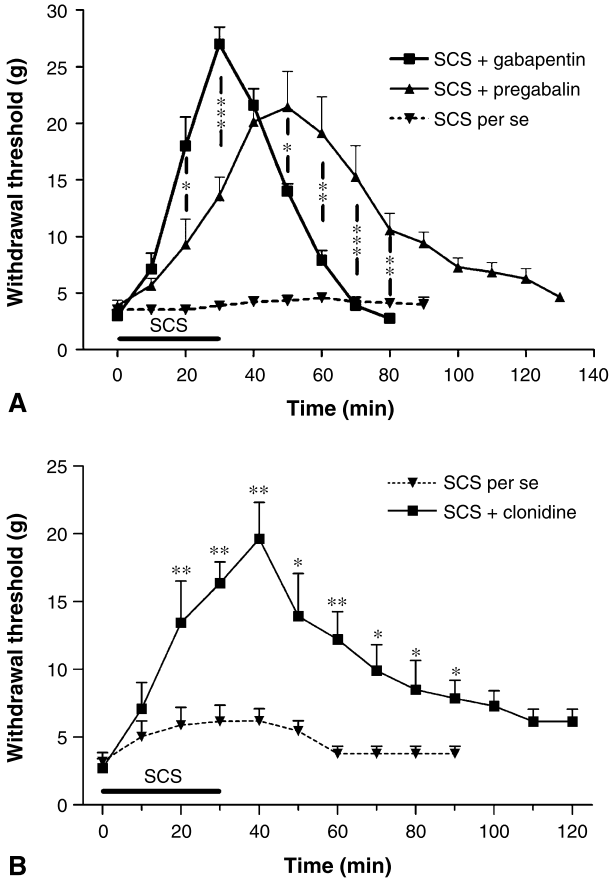

Fig. 2(A and B). Effects on withdrawal thresholds of SCS in combination with subeffective doses of (A) gabapentin and pregabalin i.t. and (B) clonidine i.t. in rats where stimulation per se was ineffective. SCS was applied for 30 min beginning at 0 min for i.t. injection. [36, 41] (*Reprinted with permission*)

ceuticals already in clinical use; gabapentin and pregabalin [41] (Fig. 2A) as well as clonidin [36] (Fig. 2B). The common denominator in these trials was that in rats not responding to SCS with symptom alleviation, intrathecal injection of a drug at a very low – and by itself ineffective dose – could enhance the effect of SCS so that the net outcome was a normalization of the withdrawal thresholds. The goal was to support SCS with such a low dose of the pharmaceutical that side-effects would be absent or only minor.

These observations formed the impetus to perform clinical trials in patients with inadequate response to SCS therapy. Since i.t. infusion of baclofen via implanted pumps has been used as treatment of spasticity [19] and adenosine has proven effective in some cases of neuropathic pain [2], it was natural to start patient trials with these compounds.

Clinical trials

Up to the present date, one formal clinical trial has been performed [21] including 48 patients of whom seven finally were implanted with SCS systems and a programmable pump for intrathecal delivery of baclofen.

The patients implanted with SCS systems combined with intrathecal baclofen administration have now been followed up for several years (in average 67 months) and some preliminary late outcome data have been accumulated.

Materials and methods

Forty-eight patients who suffered from neuropathic pain due to peripheral nerve lesions were recruited for the trial, if they proved to have insufficient effect of SCS (less than 50% pain reduction or less than 45 min post-stimulatory pain reduction after a 30 min stimulation period). Most patients had not tried SCS before entering this study thus being submitted to a percutaneous SCS trial period; however, some had been previously treated, but had experienced diminished and insufficient effect of stimulation.

In addition, some patients were tried with the intrathecal drug only. The drug baclofen was chosen to start with since we had a long experience with this drug in intrathecal pump therapy for spasticity. The same dosages for bolus trials were used as we use for regular pre-implant trials for spasticity treatment: 25, 50 and 75 µg (and for some patients 100 µg). Initially patients elected for trial received an intrathecal catheter, but as CSF-leakage-problems occurred a fine-needle lumbar puncture needle was instead used (27 G). Daily lumbar punctures with this technique were generally uneventful. Injections were given on separate days, the first dose always being the lowest, but higher doses as well as placebo (saline) were given randomly. The injections were blinded to the patients, but they were informed that one or several injections would be saline. The patients evaluated their pain using a standard visual-analogue scale (VAS) at baseline and subsequently every ½ h, to assess the effect of the intrathecal drug alone. After 1½ h a 30 min session of spinal cord stimulation was started, and the pain was again evaluated on VAS scale, as well as the post-stimulation duration of pain reduction. Only spontaneous pain was evaluated; there were no systematic tests performed for evoked pain, although in some cases the patient spontaneously mentioned decrease also of this pain component. All kinds of presumed side-effects were carefully noted. An example of a patient responding well to i.t. baclofen and SCS is given in Fig. 3.

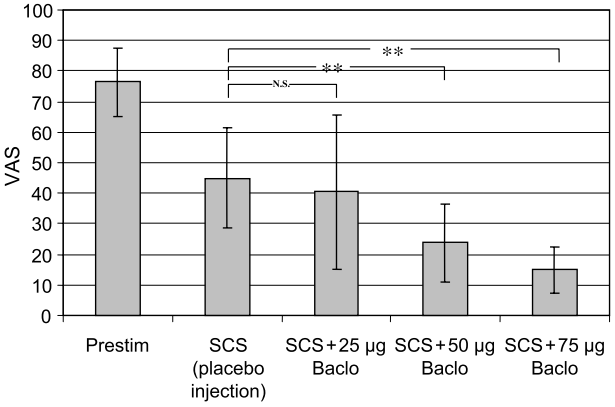

Fig. 3. Individual dose-response curve for a patient tested with SCS and baclofen. SCS at 0–0.5 h. Bolus injections were given 1½ h prior to SCS. [21] (*Reprinted with permission*)

In this study the patients were considered to have a positive response if they received a pain relief of at least 50% (with or without SCS and regardless of duration).

Seven patients were also tested for adenosine intrathecally, using doses of 500, 1000 and 2000 µg in a similar fashion, but with SCS initiated already 30 min after the i.t. injection.

Patients who benefited from intrathecal drug administration according to VAS ratings and their rating of the general effect were offered pump implantation. If the beneficial effect was mostly an increase of the effect of SCS, both an SCS-system and a pump for intrathecal drug delivery was suggested. On the other hand, if the main effect emanated from the intrathecal drug alone, only pump implantation was recommended. A few patients with effect from very low doses of i.t. baclofen were continued on peroral baclofen medication only.

Baclofen

Outcomes from the bolus trial for baclofen, in responders, are shown in Fig. 4. However out of 48 tested patients only twenty responded to the tests with pain relief of >50%. In total, 11 pumps (Synchromed, Medtronic, USA) were implanted for continuous baclofen administration. Four patients received pumps alone, without SCS, and seven both an SCS (Quad leads and Itrel 2 or 3 IPGs, Medtronic Inc, USA) system in parallel with a pump. Later two pumps were explanted, due to equipment problems and diminished therapeutic effect.

Adenosine

For adenosine delivery a different kind of implanted patient-operated pump was used, the Algomed pump (Medtronic, USA); this allows the patient to give boluses on demand by pressing a "button" placed subcutaneously. Intrathecal treatment with adenosine unfortunately often carried unpleasant side-effects, namely back-pain immediate on delivery and subsequently not rarely headache. This was possibly due to vasodilatation, and to counteract it, bupivacaine (Marcain Astra-Zeneca, Södertälje; Sweden) was added to the adenosine solution. This strategy worked well with bolus trials and the compounds injected in sequence. However, if mixed in a pump container the mixture proved to be unstable and after about a week, the pain relieving effect of bolus administra-

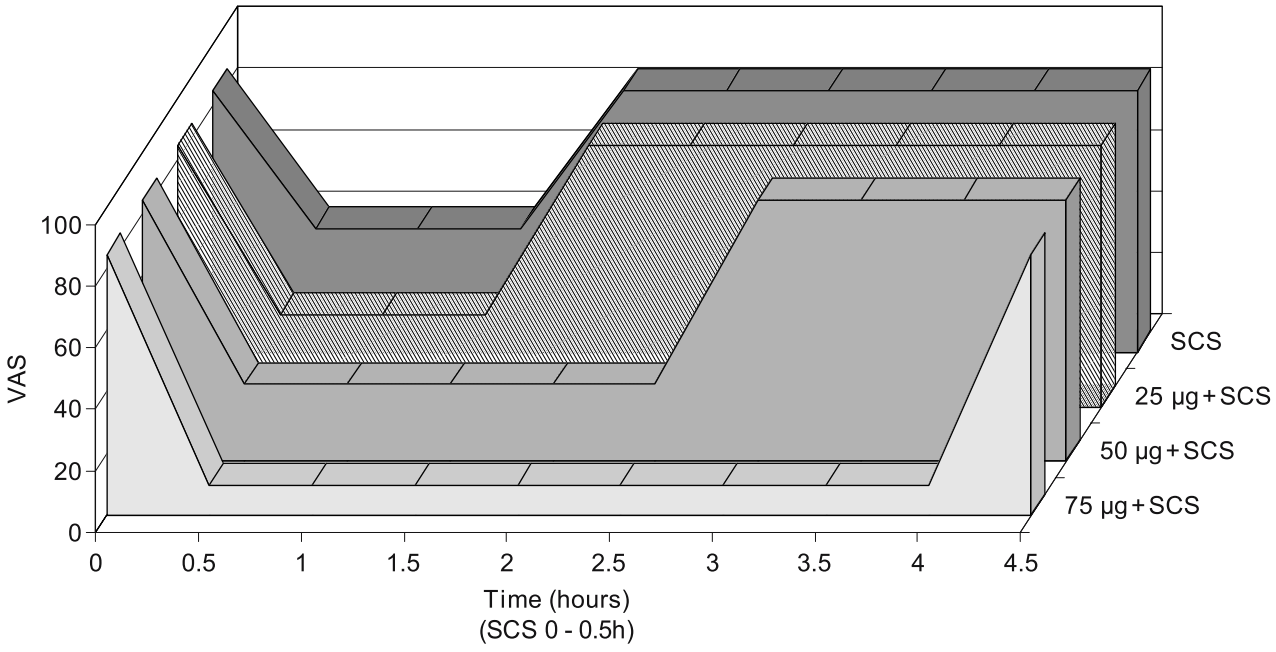

Fig. 4. Histogram, with standard deviations, of average dose-responses for 14 patients classified as responders. There is a significant difference between prestim. VAS and SCS, and a significant difference between SCS only, and SCS + 50 or 75 µg baclofen. [21] (*Reprinted with permission*)

tion performed by the patients themselves diminished markedly (>60%). Few patients, however, enjoyed good effect of adenosine and choose to use it alone in the pump without bupivacaine, but after a year they all wanted to terminate this treatment. Thus, trials with intrathecal adenosine in addition to SCS were eventually abandoned.

Results

Seven patients (average age 55) received pumps for baclofen administration as an adjunct to SCS. The starting dose of baclofen was in average 74 µg/24 h (range 50–100).

Follow-up

On the first follow-up (after in average 32 months, range 7–72 mo), the average dose had increased to 146 µg (range 75–250). Average VAS before the trial was 76 (70–90) and on follow-up 33 (0–80). Four patients (average age 53) received pumps for baclofen administration alone. Their average starting dose was 69 µg/24 h (range 50–75) and on follow-up (47 months, range 6–70) the mean dose had increased to 171 µg (range 90–290). The average VAS before the trial in this small group was 63 (40–90) and at the follow-up 33 (20–80).

Two pumps were explanted, due to diminished combined effect and subjective local irritation.

Eight of the eleven patients with receiving baclofen infusion (with or without SCS) reported one or more side-effects. These were mostly unspecific (diarrhoea, weight gain and slight numbness and heaviness of the feet). Two patients reported side-effects of sexual nature (difficulty to get orgasm (female) and impotence).

Three patients tried only low dose per-oral baclofen as an adjunct to SCS, but they all complained of tiredness and dizziness; they all chose to discontinue baclofen therapy.

Late follow-up

At the next follow-up, in average 67 months after implant, the pain-relieving effect had remained unchanged, both in patients treated with SCS and i.t. baclofen and in patients treated with i.t. baclofen alone. However a further increase in baclofen dose has been necessary for most patients (an average 30% increase of the dose at the early follow-up). Side-effects remained the same, and acceptable to all patients. No further explants have been performed. Further results from long-term follow-up will be reported in a forth-coming publication.

Discussion

Initially, the hypothesis of the combined SCS and drug therapy was developed in our laboratory as a result of two important observations [38]. First, it was observed that only a portion of rats responded to spinal

cord stimulation after sciatic nerve injury. The percentage of responders varies in different animal models but was especially low in the Gazelius model [5, 12] and in the spared nerve injury model (SNI-model) [8, 20]. This fact mimics the lack of effect in about 30 up to 50% of neuropathic pain patients, who are considered non-responders to SCS according to the criteria described above [25, 26]. Secondly, the role of the GABAergic system in SCS-induced pain relief was investigated with microdialysis techniques; this led to studies where the GABA-B receptor agonist baclofen, in a per se ineffective dose, was injected intrathecally and combined with SCS. In rats, we were able to demonstrate that the concurrent use of SCS and i.t. baclofen produced a marked potentiation of the suppression of the pain-related behaviour [4, 5], although these therapies were insufficient when used separately.

The i.t. administration of drugs in low doses requires an implanted pump and regular refills; it is, however, a logical and reasonable approach since few side effects were observed during the long-term follow-up.

The exact mechanism behind the combined effects of SCS and i.t drug injection probably varies depending on the pharmaceuticals used. In some instances a true additive effect on the receptor level is possible while in others the enhanced pain alleviation may be due to recruitment of another inhibitory mechanism.

In animal studies, it has not been convincingly demonstrated as yet that there is a programmed cell death (apoptosis) of inhibitory neurons/GABAneurons in the dorsal horns after peripheral nerve injury. It has been shown that GABAergic transmission to lamina II in the dorsal horn was clearly reduced in pain animal models displaying tactile hypersensitivity [31]. These findings suggest that the loss of inhibition resulting from disappearance of GABAergic interneurons is related to the genesis of neuropathic pain; however, these findings could not be confirmed by others [35].

In our animal studies, totally non-responsive rats proved to be good responders after bolus injections of low doses of both GABA and baclofen [4, 6]. The same has been true also for the substances investigated later such as gabapentin, pregabalin [41], and clonidine [36]. Nonetheless, it should be emphasized that in the clinical trials it was never possible to convert a totally non-responder to SCS neuropathic patient to a well responding one by adding i.t. baclofen. This is in striking contrast to the animal experimental observations and it suggests that the additive effect is more likely already exerted at the receptor level.

The microdialysis studies conducted in our laboratory showed suppression of tactile hyperexcitability by SCS; these findings have been associated with an increase in the release of GABA in the dorsal horn. In contrast, a significant decrease of glutamate and aspartate release was also related to the effect of SCS in rats in which signs of neuropathic pain were suppressed by SCS. It is important to realize that this is only one example of what is occurring in the spinal dorsal horn when SCS is applied. Most probably, a cascade transmitters release is induced of which only few have relevance to the condition treated.

Furthermore, there may be other systems involved in the effect of SCS. For example the mechanism behind the high effectiveness of SCS in CRPS is still poorly understood [22, 28]. In such pain states, there is autonomic dysregulation. This is associated not only with direct effects of SCS on hyperexcitable central neurons but also inhibitory effects on sympathetic efference as well as effects on the peripheral vasculature via other routes [26, 28].

The further exploration of physiological and neurochemical changes underlying the beneficial effects of SCS will probably provide clues to design a better pharmacotherapy when drug-enhanced SCS therapy is considered.

A ''drug-enhanced spinal cord stimulation'' trial seems to be a logical alternative for neuropathic patients with peripheral nerve injuries who lack sufficient pain relief by SCS alone or, after a successful treatment period, have experienced a reduced, inadequate effect. The substances tested so far are already registered for i.t. use. Other promising substances should be subjected to clinical trials as well; notably, a prospective randomized controlled trial with SCS and i.t. clonidine has recently been started at the Karolinska University Hospital.

One other systematic trial of baclofen as an adjuvant therapy to SCS has been started [34], but so far no results have been reported. Furthermore single patients seem to have been tried with the combination in several centres. (J-P van Buyten, pers comm). The use of intrathecal baclofen for pain therapy has been reported by many authors [1, 37, 39, 42] as well as the use of clonidine either as the only treatment [11, 14, 40] or in combination with other analgesics [9, 16].

Conclusions

In neuropathic pain patients who have an insufficient response to spinal cord stimulation, a trial with intrathe-

cal drug administration aiming in enhancing the effect of SCS may be warranted. Such a trial can be performed both in patients undergoing first-time testing for SCS as well as in patients who have already received SCS but continue to experience a diminished effect. A number of patients may benefit from the combination of SCS and intrathecal drug delivery; it is necessary that patients are aware of possible side-effects as well as the need for frequent health care contacts necessary to maintain the intrathecal drug-delivery system. The combination of SCS and peroral baclofen has not, so far, been proven effective considering the side-effects reported in our few cases and also from personal unpublished reports from clinical colleagues. Systematic trials with peroral gabapentin and pregabalin in low doses seem warranted. However, to our knowledge, they have not yet been performed. In Fig. 5 we propose an algorithm for testing adjuvant intrathecal therapy in cases of inadequate effect of SCS alone. Further preclinical and clinical research in this area could contribute to develop a combined SCS-drug treatment in neuropathic pain patients.

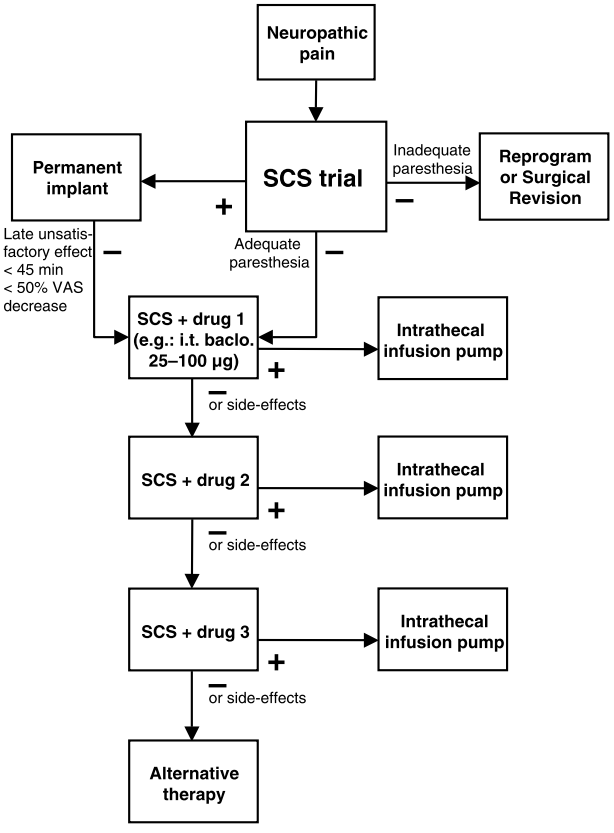

Fig. 5. A suggested algorithm for trial of SCS and intrathecal drug therapy

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Neurosurgical pain therapy with epidural spinal cord stimulation (SCS)

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Summary

Neurosurgical therapy for intractable pain with epidural implantable electrodes has become a widely used and efficient alternative when conservative or less invasive therapies are no longer effective. A complete interdisciplinary work-up is required before considering a patient as a candidate for a spinal cord stimulation (SCS) device. In more than 1300 patients we implanted an SCS device in our clinic; more than 52% reported a significant (>50%) long-term improvement for more than 3 years and a significant reduction in their analgesic drugs. Although placement of the electrode and implantation of the stimulator are technically easy to perform, they do carry a risk of potentially debilitating complications such as meningitis or component migration. Hence, SCS therapy should only be performed in specialized centers. In peripheral vascular disease (PVD) and angina, the initial results are very promising, but the long-term efficacy has to be proven by multicenter studies.

Keywords: Neuromodulation; pain; failed back syndrome; spinal cord stimulation; SCS; epidural stimulation.

Introduction

Electrical stimulation for intractable pain syndromes is not a new therapy. In the 17th century, Descartes proposed that pain was a specific sense of its own, mediated by its own central and peripheral apparatus like taste, smell, and hearing. In the 19th century, pain was considered as the result of an intense stimulus mediated to the brain by non specific receptors. One theory suggested the existence of specialized local receptors, the other a specific pattern of information, a quality determined by the intensity of the stimulus.

In 1965, Melzak and Wall proposed the ''gate control'' theory [12] and described a sensory discriminative system that reports the location and intensity of a stimulus to the brain, as well as a motivational-affective system, that reports on the quality of pain. Melzak and Wall used the symbol of gates letting in or keeping out pain in varying degrees. In this model, the personality of the patient has a great impact on the intensity of the perceived pain. Pain is a result of present and past experiences and perceptions, which may be conscious or unconscious. The ''gate control'' metaphor may help explain why the same injury can be experienced so differently among various people. After the first implantation of a spinal electrode by Shealey and Mortimer in 1967, neurosurgeons became interested in electrical stimulation therapy [8]. In 1969, Reynolds *et al.* were able to show that electrical stimulation of the brain stem could provoke profound analgesia in laboratory animals [20]. Since then, neurostimulation has been applied to every location along the pain pathway: dorsal column stimulation (DCS), spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), deep brain stimulation (DBS in brainstem or thalamus), and motor cortex stimulation (MCS) [1, 3, 8, 16]. This widespread clinical application somehow contrasts with very few convincing experimental studies examining the mechanisms of stimulation induced analgesia. In 1993, Kupers and Gybels [11] showed that thalamic electrostimulation is able to reduce mechanical allodynia produced by partly ligating the sciatic nerve in a rat model of neuropathic pain. This effect could not be reversed by the application of naloxone, suggesting a non-opioid mechanism of pain modulation. In SCS, nerve fibers near the dorsal column of the spinal cord are stimulated, thereby masking the sensation of pain. SCS stimulation also provokes a heat sensation; this is due to an increase of blood flow to the affected skin area resulting in a local temperature increase and hence stimulating peripheral thermoreceptors.

Table 1. *Main indications for epidural spinal cord stimulation*

– radicular pain
– failed back surgery syndrome (FBSS) with neuropathic pain
– chronic sciatic pain due to epidural fibrosis or aseptic adhesive arachnoiditis
– complex regional pain syndrome (CRPS I)
– phantom limb pain
– peripheral vascular disease (PVD)
– angina

Patient selection for SCS

Clinical conditions that represent widely accepted indications for SCS implantation include: failed back surgery or low back syndrome, radicular pain syndrome or radiculopathies resulting in pain secondary to failed back syndrome, herniated disk pain refractory to conservative and surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis, complex regional pain syndrome, reflex sympathetic dystrophy or causalgia, stumb pain, angina and PVD (Table 1) [2, 5, 8, 10, 13, 16, 19, 23, 24]. SCS should be applied only if other conservative and less invasive approaches have failed. If there is radiological evidence of spinal canal or root compression, microneurosurgical decompression is indicated but not SCS. Up to now, no defined clinical pattern has been found to predict pain relief by SCS. Nevertheless, clinical data indicate that neuropathic pain is more accessible by SCS than nociceptive pain. SCS produces a segmental, reversible inhibition of sympathetic vasoconstriction in the periphery. Many patients report a comfortable feeling of warmth and stimulation induced paresthesias in the corresponding area. In order to achieve suppression of pain perception, switching on the electric current in SCS stimulation should result in tingling sensations that cover the painful regions and dermatomes [7]. Since 1977, spinal epidural electrodes have been implanted in more than 1300 patients at the Department of Stereotaxy and Functional Neurosurgery in Cologne for the treatment of chronic pain. Of these patients, 80% suffered from lumbar pain with or without pain radiating into the lower extremities (ischialgia).

SCS implantation is not indicated if there is a history or clinical evidence of serious cognitive deficits, poor compliance with treatments, addiction to alcohol or other drugs, suicidal tendencies or psychosis. On the other hand, using detailed psychological testing, we were not able to prove whether psychosocial factors such as social support, family status, religion, depression, attitude towards the disease, coping, personality type, and overall satisfaction concerning work and private life have predictive value with respect to the efficacy of SCS. Preoperatively, patients are asked to draw a ''body map'', showing all body regions affected by pain and to fill out a ''pain diary'' for a few weeks before and after implantation. In addition, patients undergo an MRI study to exclude any surgically curable cause of pain such as disk prolaps, spinal stenosis, etc. Based on our experience, the best indication for SCS seems to be long-standing severe leg pain.

Technical aspects

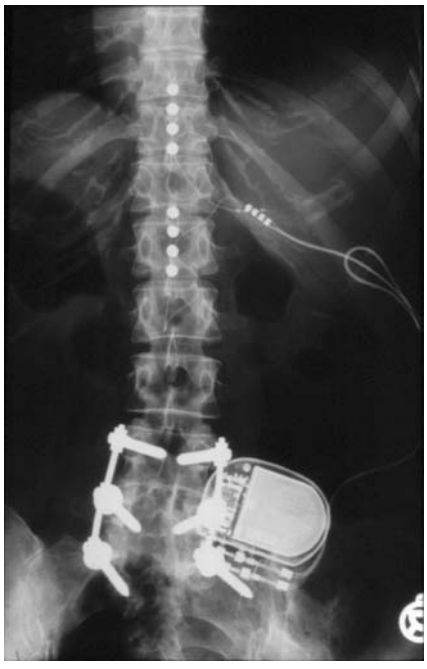
The first SCS system was implanted in 1967. Since then, the technology has undergone significant developments, including advances and refinements in equipment design, flexibility, reliability, and lifespan. At present, several different companies manufacture a variety of SCS systems (Fig. 1a). In certain types of stimulators, a radio-frequency receiver is implanted and the power source is carried externally with the aid of a belt. This has the advantage that batteries can easily be re-charged when getting empty but the disadvantage of cumbersome external components. In systems where the power source (battery) is implanted, there are no external components. However, when the battery is empty, it must be replaced by performing a small operation under local anaesthesia.

Concerning stimulating electrodes, there has been a trend away from plate electrodes implanted under general anaesthesia following laminectomy to small ring electrodes that are implanted by minimally invasive puncture under local anaesthesia [14]. Similar to most surgeons [15, 19, 21, 23], we prefer a staged procedure. The first stage includes implantation of the electrode and testing with an external stimulator; after a successful trial period of 7 days in our clinic, the second stage involves the implantation of the generator.

SCS implantation: surgical aspects

Preoperatively before SCS implantation, a complete blood count and urine analysis should be conducted on an outpatient basis to exclude acute infections and clotting disorders. Preoperative education of the patients and their informed consent for the procedure should be carried out by the implanting surgeon. Information should cover all preoperative aspects, the implant procedure, all potential risks associated with the surgery, the postoperative management, possible postoperative pain or discomfort, postoperative precautions, self-care responsibilities, and follow-up care.

a



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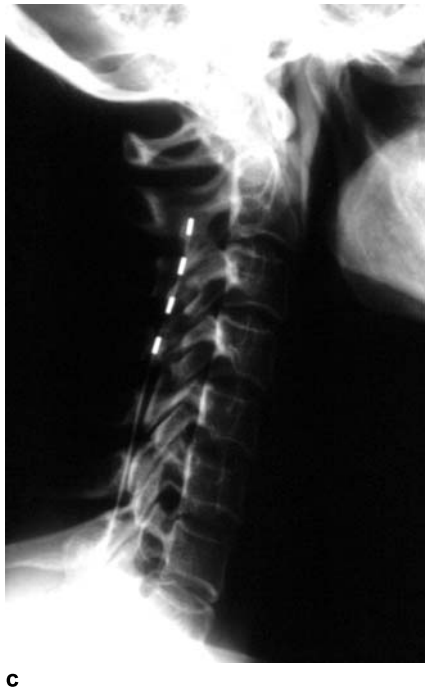

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Fig. 1. (a) Different types of SCS electrodes designed for implantation following either a laminectomy (left) or puncture (right). (b) Postoperative X-ray of a patient with intractable lumboischialgia. The stimulator is attached to eight epidural electrodes located at L1 and Th11 via subcutaneous wires and a connector. (c) Lateral X-ray of four cervial epidural SCS electrodes that were implanted transcutaneously and minimally invasively at the level C3–C4

Puncture of the lumbar area and electrode implantation is performed under local anaesthesia. A ''loss of resistance'' after perforation of the ligamentum flavum and the expected negative pressure may be helpful in indicating the epidural space. The electrode is advanced cranially under fluoroscopic guidance and connected to an external stimulator. The exact position of the lead should be adjusted so that under stimulation a comfortable paresthesia covers the whole painful area. When the final electrode position is reached, we perform an-

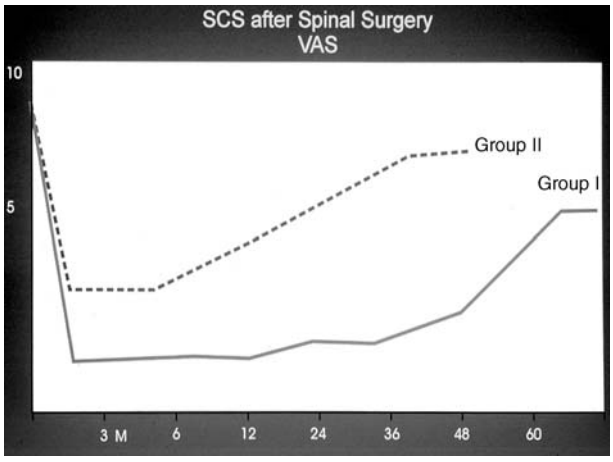
other x-ray to document this position for future reference (Fig. 1b and c). Thereafter, the percutaneous extension wire is connected and sterile dressings are applied. We perform an intensive trial period over the following 5–7 days and the patient assesses the efficacy of SCS stimulation on his/her particular pain syndrome. About 20% of our patients did not respond satisfactorily to SCS during this trial period (''non- responders''). In such patients, permanent implantation is not indicated and the electrode is removed. A permanent implantation of pulse-generator may be performed in patients in whom pain relief is at least 50% during the trial period. We create a subcutaneous abdominal pocket for the permanent implantation of the generator in the lateral wall below the rib cage and above the belt line.

Side effects and complications

Since electrical stimulation is reversible and can be adjusted by meticulous postoperative programming of the device, the side effects of SCS did not represent a significant problem in our patients. Technical complications were more common than medical ones. In the clinical course of a patient, a change in the distribution of induced paresthesias may indicate migration of the electrode. In contrast to electrodes implanted after laminectomy, percutaneously implanted electrodes cannot be fixed in place securely. Electrode dislocation, when it occurs is most common in the first four weeks after implantation. After this period, the tip of the electrode is kept in place by connective tissue. Electrode migration or dislocation occurred in about 10% of patients in a follow-up of 8 years.

Long-term results

Patients who experience a reduction of pain intensity by at least 50% on the visual analogue scale (VAS) are generally defined as ''responders''. In 64.4% of patients with permanently implanted SCS systems, pain relief was good/excellent (>50%, group I) (Fig. 2a–c). In 35.6% of permanently implanted patients, pain relief was moderate/poor (<50%, group II). The mean VAS in group I was 9.6 preoperatively and 1.8 postoperatively in a follow-up of five years. In Group II, the mean preoperative VAS was 9.6; it was reduced to 3.0 during the first six months and increased to 6.0 over the following three years. All patients were treated with analgesics preoperatively. In Group I, we observed a significant drug reduction. We did not observe a significant long-term



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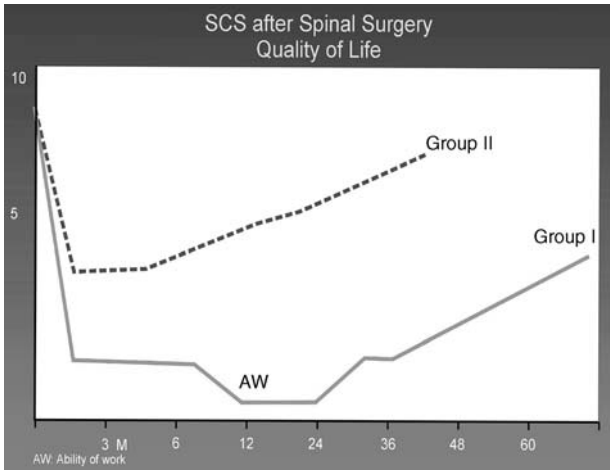

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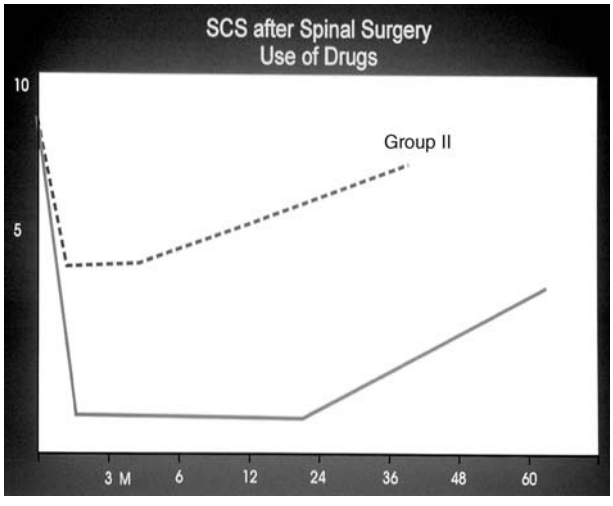

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Fig. 2. (a–c) Long-term effect of SCS therapy on pain (*VAS*), quality of life and analgetic drug intake in patients with ''failed back syndrome'' (*FBS*). *Group I* ''responders'', pain relief >50%; *Group II* non-responders pain relief <50%

reduction of analgesic drugs in Group II. Concerning the postoperative quality of life, in Group I we observed significant improvement from a mean of 1.8 to 3.7 after five years. Many patients were able to return to work. In Group II, the positive effect on quality of life was only temporary and ceased after six months. In general, 52% of all patients reported a significant long-term improvement of pain as assessed by VAS and a significant decrease on analgesic drug consumption due to SCS (Fig. 2a and c).

SCS for intractable angina

Intractable angina is defined as coronary heart disease of grade III–IV according to the Canadian Cardiovascular Society (CCS) classification with increasing symptoms under medical combination therapy [6]. On the basis of the ''gate control'' theory, neurostimulation may relieve angina by activation of myelinized sensory fibers, thereby blocking the nociceptive activity of thin and non-myelinated fibers in the dorsal horn. Another effect of SCS in angina is the reduction of the sympathetic tone. In 1998, Norrsell *et al.* [13] found a significant reduction of blood norepinephrine levels after SCS (18% versus 47%). By 2002, more than 2000 patients with intractable angina had been treated with SCS. The technique of electrode and generator implantation is similar to the one described above, except that the target point for the electrode tip is at the level of T1-2. Electrodes may vary in size. Larger electrodes and electrode spacings can be used to cover several vertebral segments and broaden the pattern of stimulation. To qualify for SCS therapy, patients should present with severe and stable angina pectoris, markedly reduced quality of life, stenosis of the coronary arteries on coronary angiography, pain refractory to optimal medical treatment, no interventional possibility for revascularization, and have a positive attitude regarding implantation. The option of revascularisation should be excluded by coronary angiography. Patients who have unstable angina, valve defects or reduced compliance are not candidates for SCS implantation. Cardiac pacemaker systems may interfere with the SCS system and vice versa thus excluding these patients as candidates for implantation. In the last 24 patients who were implanted at the Department of Stereotaxy and Functional Neurosurgery [4, 5], after 12 months of therapy with SCS, nitrate medication was reduced significantly from 5/day to 0.4/day on average. Ergometric testing values increased significantly from 65 to 94 watts on average. Distance of the standardized 6-minute walking test increased significantly from 143 to 258 m after twelve months on average. No serious complications were observed in these patients. The most common complication of the procedure was electrode dislocation, which made operative re-positioning necessary in four patients. It is important to point out that although SCS reduces significantly the pain in patients with angina, it does not suppress the acute pain from cardiac infarction; therefore, it represents an important alternative when medical or interventional therapies are no longer effective.

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Spinal cord stimulation for failed back surgery syndrome and other disorders

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Summary

Chronic pain is a complex condition that requires a multi-disciplinary approach to management. Spinal cord stimulation (SCS) has evolved into a relatively easily implemented, reversible technique with low morbidity for the management of chronic, intractable pain in selected patients. Percutaneous placement of electrode arrays, under local anaesthesia, supported by programmable, implanted electronics has been a major technical advance.

Multicenter prospective studies were conducted and demonstrated that SCS, as a neuromodulation procedure, is indeed a superior method for treatment of chronic pain if the patients are selected with caution and a proper strategy. Future development of innovative electrodes and pulse generation systems will continue to improve this therapy.

Keywords: Spinal cord stimulation; SCS; trial; chronic pain; failed back surgery syndrome; intractable angina; chronic regional pain syndrome; CRPS; neuropathic pain.

Introduction

Spinal cord stimulation (SCS) has been in clinical use for the treatment of non-malignant chronic pain for over 30 years. Its mechanisms of action remain poorly understood, in spite of very detailed understanding of the anatomy and physiology of the dorsal horn and of central and peripheral pain pathways. A great deal has been learned over the last three decades about the clinical applications of SCS in terms of indications for use and implantation techniques, and huge technological advances have been made in the hardware that is used. With appropriate patient selection and well-positioned electrodes, pain control with SCS can be excellent and can lead to significant improvement in quality of life for chronic pain patients.

History of spinal cord stimulation

Electrical stimulation has been used in various different forms, and with varying degrees of success, by many different cultures for the treatment of painful conditions for thousands of years. Natural sources of electricity such as the torpedo fish (named from the Latin 'torpedo' meaning 'numbness') were used to treat conditions as diverse as gout and headache. The advent of the ability to store and generate electricity in the 18th century led to the widespread, and somewhat indiscriminate, use of electrical stimulation for painful conditions. Limited success, and not infrequent disasters, resulted in the prohibition of the technique at the beginning of the 20th century, by which time advances in pharmacology were changing the face of pain therapy.

In 1959, it was reported that paraesthesia produced by electrical stimulation of major nerve trunks was associated with anaesthesia and analgesia in the distribution of the peripheral nerve [1]. This observation went largely unnoticed until the publication of the Gate Theory in 1965 [20].

The Gate Theory provided the first real scientific basis for the use of electrical stimulation for pain. It postulated that the perception of pain could be modified by input from larger diameter sensory fibres. The theory was applied first to percutaneous stimulation of peripheral nerves [34] and implantable peripheral nerve stimulators soon followed [31].

The American neurosurgeon Norman Shealy postulated that applying stimulation directly to the dorsal columns might be a more effective way to 'close the gate' in the treatment of chronic pain. His suggestion was received with a certain degree of scepticism at first, but he persisted and implanted the first spinal cord stimulator in 1967 [28]. Results were initially encouraging, and this led, inevitably, to numerous stimulators being implanted for various poorly defined indications, and

therefore to poor overall results and a decline in interest in the technique.

Fortunately the technology continued to advance. It became clear that leads could be placed epidurally rather than subdurally [7] and then the percutaneous technique of insertion was developed [8, 11, 29, 35]. Improvements in technology led to better results and fewer complications, and spinal cord stimulation became more widely accepted.

Modern spinal cord stimulators can be either completely internal or have both internal and external components. With a completely internal system the battery-powered pulse generator is surgically implanted. This has obvious advantages for the patient but does necessitate re-operation to replace the battery every few years. The other option has an external power source which the patient needs to wear; such systems are used less commonly than the fully implanted variety but may be useful where very high demands are being made on the power supply and an implanted battery would require changing too frequently.

Neuroanatomy and physiology

Different types of primary afferent fibres convey information about different sensory modalities. The large diameter myelinated fibres are: Ia afferent fibres from muscle spindles; Ib afferents from Golgi tendon organs; II afferents from secondary sensory endings. Smaller diameter fibres are: Aδ fibres (myelinated) conveying nociception and temperature; C fibres (unmyelinated) conveying somatic and visceral information.

Nerve endings of the different primary afferent fibres have characteristic distributions within the dorsal horn. Cutaneous mechanoreceptor primary afferent terminals are almost exclusively ventral to the border between lamina II and lamina III. Aδ fibres terminate mostly in lamina I and also in lamina II; collaterals from the lamina I terminals extend down to lamina V – the site of second order spinothalamic tract neuronal cell bodies. Somatic C fibres input predominantly to the deep part of lamina II and also to lamina I. Visceral C fibres terminate much more diffusely in laminae I, II, V and X and also contralaterally in laminae V and X. The diffuse nature of visceral fibre termination is part of the anatomical basis for the poor localisation of visceral pain.

On entering the spinal cord, primary afferent fibres may project over as many as five segments either side of their point of entry. This is presumably why the topographical distribution of paraesthesia resulting from spinal cord stimulation does not correspond well with anatomical dermatomes [32].

The distribution of neurotransmitters within the dorsal horn is also non-random. It is likely that different sensory modalities use different combinations of neurotransmitters. This hypothesis has proven very difficult to demonstrate but patterns are beginning to emerge.

The anatomical basis of the gate theory is the modulation of the nociceptive input to lamina V neurones (second order spinothalamic tract) by large diameter myelinated fibres. Collaterals from dorsal column 'touch' fibres synapse with interneurones in lamina II, thereby inhibiting spinothalamic neurones, probably by presynaptic inhibition.

The larger the diameter of a fibre, the lower its activation threshold, therefore tactile and proprioception fibres can be recruited selectively by electrical stimulation. The maximum depth of stimulation is believed to be about 0.25 mm [12]. The amplitude required for stimulation of an individual fibre is inversely proportional to the diameter of the fibre and its distance from the electrode. This should mean that SCS is relatively selective for the dorsal columns, however we have found that stimulation can be effective even when the electrodes are positioned *below* the level of L1, implying that large diameter fibres in the cauda equina rootlets can also be affected by SCS.

Applications and patient selection

Failed back surgery syndrome is currently the commonest indication for SCS. Many studies have looked at SCS for failed back surgery syndrome and most report a success rate of about 70% [23]. A recent randomised controlled trial by North *et al.* has shown SCS to be superior to repeat surgery [22] for persistent or recurrent radicular symptoms after lumbosacral spine surgery (excluding patients with gross surgical pathology), and is highly likely to obviate the need for any further surgical intervention. A further randomised controlled trial comparing SCS to best medical management for failed back surgery syndrome is currently underway [16]. In general it is more difficult to achieve good pain control in the region of the lower back than in the extremities; advances in lead design are leading to improved results in this area. Dual leads have advantages in the treatment of axial low back pain.

Other conditions that may respond to SCS include angina pectoris, ischaemic and phantom limb pain, complex regional pain syndrome (CRPS), spinal cord injury and peripheral neuropathies and plexopathies. In gen-

eral, neuropathic pain is likely to respond better than nociceptive pain [2–5, 9, 10, 13, 17, 19, 21, 23, 24, 26, 27, 30].

The reported efficacy of SCS varies depending on the condition being treated. There are few large series looking at SCS for indications other than failed back surgery syndrome. Sanchez-Ledesma *et al.* reported their results for 24 patients who had undergone SCS for CRPS. Nineteen patients had successful trials and of those patients, all reported at least 50% improvement and 89% reported excellent pain relief in the long term [27]. Broseta *et al*. [6] looked at SCS for post-amputation pain and found all their patients obtaining good pain relief in the short term and 73% maintaining good pain relief at long term follow up.

Ischaemic pain, and particularly ischaemic rest pain, is another primary indication for SCS. SCS has been shown to improve peripheral blood flow [8], presumably by suppressing sympathetic vasomotor control [14, 18]. SCS is therefore most effective where there is a reversible element to the ischaemia, rather than in patients where the principal problem is atherosclerotic disease. Vasospastic diseases such as Raynaud's and collagen disorders respond well, as does pain associated with diabetic arteriopathy. Improved peripheral blood flow can improve ulceration associated with ischaemia, and even improve chances of limb salvage [14].

SCS is indicated for the treatment of angina pectoris in patients who are refractory to medical therapy and are either not candidates for coronary revascularisation surgery or who have relapsed after surgery. Unlike in the case of peripheral vascular disease, SCS has not been shown to improve coronary blood flow, and its exact mechanism of action in treating angina pain is not understood.

A number of criteria need to be fulfilled before a patient can be considered for spinal cord stimulation. The majority of patients are referred from pain clinics and will have tried most other treatment options already. Different units will have their own selection processes, but the criteria published by Krames in 1996 [15] for selecting patients for intraspinal opioids are very useful:

- more conservative therapies have been unsuccessful
- there is an observable pathology that fits with the patient's symptoms
- there are no other surgical options
- there is no concern regarding drug misuse by the patient
- the psychological profile of the patient is appropriate
- there are no contraindications to implantation (e.g. coagulopathy, intercurrent infection)
- the patient has undergone a successful trial of the therapy

It is, of course, essential that coverage of the area of the patient's pain should be technically feasible. Previous Doral Root Entry Zone lesioning is a contraindication, as is spinal cord injury *above* the intended level of stimulation.

Neurostimulation hardware

A spinal cord stimulator consists of one or more electrode arrays positioned on the dura over the dorsal columns. The leads are connected to the battery-powered neurostimulator [also called an implantable pulse generator (IPG), or simply 'battery'] by extension wires. (NB the terms 'lead' and 'electrode' are often used interchangeably).

Leads can be implanted percutaneously, or surgically by a small laminotomy. Percutaneous leads available currently are cylindrical. The contact array can have either 4 electrodes (quadripolar) or 8 electrodes (octapolar).

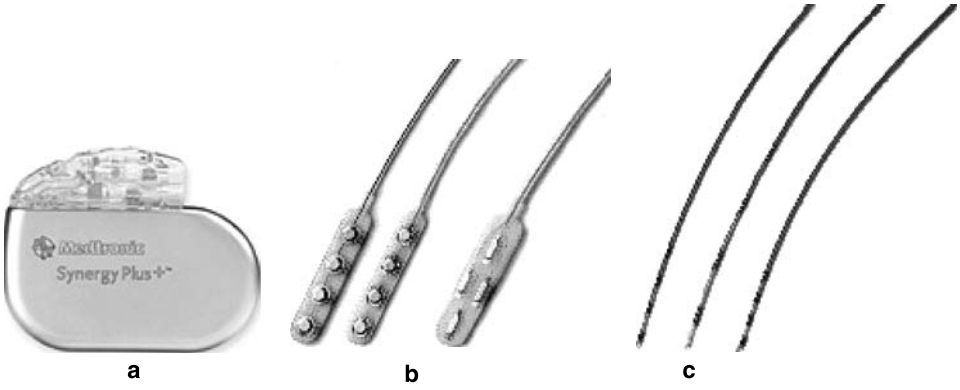

Fig. 1. (a) IPG *Synergy Plus* (Medtronic). (b) Surgical plate electrodes (Medtronic). (c) Percutaneous electrodes (Medtronic). (Pictures reproduced with kind permission of Medtronic, Minneapolis, MN, USA)

Surgically implanted leads are flat 'plate' arrays and are also either quadripolar or octapolar. Any combination of electrodes can be employed to achieve the best possible coverage for the patient, provided that at least one electrode is positive and at least one is negative.

There are three basic parameters which the surgeon can alter in order to optimise pain control: pulse width, rate and amplitude. The pulse width is the duration of each pulse of stimulation in microseconds. Widening the *pulse width* will increase the area of tissue being stimulated and strengthen the degree of paraesthesia experienced by the patient. The *rate* is the frequency at which the pulses are delivered and is measured in Hertz. Varying the *amplitude* alters the intensity of paraesthesia that the patient experiences. Pulse width, amplitude and rate should all be set at the lowest effective level in order to maximise battery life.

IPGs can be programmed once implanted by using an external 'wand'. Patients are provided with a simple device that can adjust the amplitude, pulse width and rate, and turn the stimulator on and off.

Stimulation can be continuous or cycling. Having the stimulator in cycling mode means that there are specified on and off times, e.g. 30s on and 30s off. The advantage of using cycling mode is that it can increase battery life significantly. In general, continuous mode is used initially so that the patient can get used to the stimulator, and then cycling mode can be tried later on.

Operative technique

Stage one involves the implantation of the lead for the trial period. The procedure is carried out under local anaesthetic wherever possible in order to allow feedback from the patient. This is usually not a problem with a percutaneous technique, but general anaesthesia will often be required for implanting surgical leads.

Prophylactic antibiotics should be given. The patient lies prone on an X-ray table and the skin around the insertion site is cleaned with surgical prep solution and anaesthetised with local anaesthetic. The level of entry is obviously dictated by the level of the patient's pain, e.g. for coverage of the back and lower limbs the tip of the lead should lie at about T10 and therefore the entry point on the skin will be about L3–L4. An incision is made approximately 2 cm lateral to the midline at the desired level of insertion. A Tuohy needle is inserted obliquely into the epidural space under fluoroscopic guidance and then the lead is passed down the needle and advanced under fluoroscopic guidance until the appropriate level of the spinal cord is reached. For bilateral symptoms one should aim to have the lead in the midline. For unilateral symptoms the lead should lie slightly towards the affected side. Steering the lead can sometimes be a little awkward, especially if there has been previous surgery and there is epidural scarring. Manipulation of the Tuohy needle, and sometimes putting a slight bend in the lead itself, can help to achieve the correct position.

Once an appropriate position has been achieved the epidural lead is connected via an external lead to the external stimulator and switched on. Different combinations of electrodes, pulse widths, rates and amplitudes can then be tried to find the optimum settings for the patient. The position of the lead itself can be adjusted as necessary. An X-ray should be taken recording the final position of the epidural lead.

The epidural lead is connected to a temporary extension lead, which is tunnelled about 10 cm from the needle insertion site and externalised. The epidural lead is anchored to the thoracolumbar fascia and the electrical contacts are covered with a plastic 'boot' which is secured in place with a non-absorbable braided suture. The patient is given instruction in the use of the external stimulator to allow them to alter the stimulation settings during the trial period.

The technique for implanting the surgical electrode follows exactly the same principle as for the percutaneous lead. The procedure may be carried out under local or general anaesthesia. The spine is exposed at the appropriate level by standard technique, and then a small laminotomy made to allow the electrode to be placed on the dura under fluoroscopic guidance. The electrode is secured and the external leads are then connected and tunnelled in the same way as for the percutaneous lead.

Patients are assessed at the end of the trial to determine whether pain relief is sufficient to justify proceeding to implant a permanent neurostimulator. In our unit patients are reviewed at one week, and if the stimulator is obviously beneficial the trial is terminated; where the benefits are less certain the trial period is extended to two weeks. Criteria differ from unit to unit as to which patients should undergo implantation but generally one would look for a minimum of a 50% reduction in reported level of pain. The wires that have been externalised should be pulled taut and cut flush with the skin, so that the cut ends retract below the skin surface. The whole system is then left for a minimum of four to six weeks to allow it to sterilise, in order to minimise the risk of infection when the permanent device is implanted.

Stage two involves implanting permanent extension leads and the IPG. Implantable pulse generators currently available are about $7 \times 5 \times 2$ cm, depending on the model. The IPG will be visible under the skin in thin to average patients and it is important to discuss the site of implantation with the patient beforehand. It is especially important to ensure that the device will not be in a site where it may rub against the arm of a wheelchair or against a belt. The most common sites for IPG implantation are the anterior abdominal wall and the buttock. IPG implantation can be carried out under general anaesthetic, as there is no requirement to test the system during the procedure. The paraspinal incision is re-opened and the temporary extension leads changed to permanent leads of a length appropriate to the intended site of implantation of the IPG. A subcutaneous pocket is fashioned for the IPG and the extension leads are tunnelled to the pocket and connected. The incisions are closed in a standard fashion.

Changing the IPG when the battery runs out is straightforward. The extension leads do not require replacing so it is usually possible to do the procedure under local anaesthetic, with prophylactic antibiotic cover.

As technology improves the dimensions of the IPGs will hopefully reduce, making the device more comfortable for the patient. Unfortunately, increasing complexity of the electrode arrays themselves has resulted in the need for greater power from the battery, thereby making reduction in IPG size even more of a challenge!

IPGs that can be recharged *in vivo* have recently become available, with the obvious advantage that battery life is considerably longer (expected to be at least 9 years in the average patient). Rechargeable IPGs are significantly more expensive than non-rechargeable ones, however the increased life span may justify the extra cost in the long term.

Complications

The overall risk of complications with spinal cord stimulation is low. Problems can be associated with insertion technique, the components used and with the stimulation itself.

As with any implant, the most important complication is infection. The reported rate of infection is about 5% [33]. Minor infections can be managed with antibiotic therapy but more serious infection can necessitate removal of the device. Fortunately, infection involving the epidural component is extremely rare, and it is usually sufficient to remove only the IPG and extension lead.

Other complications associated with insertion are rare and include cerebrospinal fluid leak, epidural haematoma, and injury to the spinal cord or nerve roots.

Component failure is also uncommon. Perhaps the most frequent problem with the epidural leads is migration (although this has become less common with modern equipment); this may necessitate repositioning, or even changing to a plate electrode, which can be secured to the dura. Movement of the electrodes may result in alteration in the area of stimulation. One patient in our series who had a lead implanted in the thoracic spine found that the distribution of stimulation moved from one side of the body to the other when walking. In such cases it is worth trying surgically implanted plate electrodes, as they can be anchored to the dura and are therefore less prone to migration. Actual component failure used to be a not infrequent occurrence but is rare with modern devices.

Changes in stimulation associated with changes in posture can be a problem for some patients. This does not arise from migration of the lead, but is due to the alteration in the distance of the lead form the spinal cord due to CSF displacement during movement. Alteration of stimulation parameters, and especially the ability of the patient to adjust the stimulator settings, can help to minimise this problem.

Efficacy

The majority of patients who undergo a successful trial and go on to implantation continue to benefit from SCS in the long term. It is rare in our experience for patients to discontinue using the device, and only a very small number of patients request removal of the device. Reported rates of technique failure vary considerably. Where it is necessary to remove the stimulator we would tend to remove only the IPG, leaving the extension leads and epidural component in situ.

There are four main reasons why SCS may fail: progression of the condition, development of tolerance to the stimulation, component failure and pain at the site of implantation [25]. Progression of the disease may result in pain in areas not covered by the simulation. Alteration of the settings can compensate for this to some extent but it may be necessary to reposition the electrode. Pain at the implantation site may necessitate moving the IPG.

Newcastle General Hospital series

The first SCS trial in our unit was carried out in 1993 and a total of one hundred and twenty patients (seventy-

one male and forty-nine female) have undergone the procedure to date. The average age at surgery was 51.5 years, with a range from twenty-four to seventy-four years. The commonest indication has been failed back surgery syndrome, which accounts for 45% of the total number of trials. Other indications were intractable angina pectoris (17.5%), peripheral vascular disease and Raynaud's syndrome (5%), complex regional pain syndrome (7.5%) and other types of neuropathic pain (25%). Patient follow-up is at a nurse-led pain clinic as well as the surgical outpatient clinic. The trial period is usually one week, extended to two weeks where there is any debate as to efficacy. Following implantation, regular follow-up allows adjustments to be made to the various parameters as necessary. Ninety-six patients (80%) reported reduction in pain of at least 50% during the trial period (based on the visual analogue pain score), as well as significant improvement in function. All patients reporting a 50% or greater reduction in pain went on to have implantation of the pulse generator (done under general anaesthesia). Complications have been few, with one abdominal wound haematoma (managed conservatively), one wound infection (managed with antibiotic therapy alone), four cases of electrode migration, three cases with lead failure and two cases with stimulation-related complications (uncomfortable paraesthesiae or increase in pain). We have also re-sited one IPG because of discomfort.

Future developments in spinal cord stimulation

At the time of writing, the principal indication for SCS is failed back surgery syndrome. There are few randomised controlled studies in the literature, making it difficult to be certain of the place of SCS in the treatment of other types of chronic pain. Advances in technology should allow better coverage, smaller IPGs, fewer problems with lead migration and malfunction, and longer battery life.

The cost of SCS is a significant factor in limiting its use at present. When considering this, it is important to take into account that successful SCS treatment should obviate the need for further surgical procedures. Fixation systems for spinal stabilisation in failed back surgery syndrome, and the theatre and in-patient time associated with their use, are far from inexpensive! Successful treatment of chronic pain should also result in significant functional improvement for the patient, including the possibility of return to work. When the cost is calculated over the life span of the stimulator, SCS is in fact *less* expensive than other treatments for chronic pain.

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Spinal cord stimulation for the treatment of chronic non-malignant pain

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Summary

Over the past four decades, techniques and devices for spinal cord stimulation have undergone considerable refinement. Currently, percutaneous implantable electrodes are placed in the epidural space and a low-frequency electrical current is used to modify the transmission of chronic pain signals in the dorsal columns of the spinal cord.

Before permanent implantation, the spinal cord stimulation will be examined during a test phase to determine its analgesic effect and tolerability.

We have reviewed our experience in 88 patients with chronic non-malignant pain. The follow-up of our study ranged from 15 to 75 months, with an average of 60 months.

The indication for SCS in these 88 patients was mainly neuropathic pain syndromes.

The patients were followed up by the Visual Analog Scale (VAS), level of activity and subjective assessment of the quality of life. On the basis of the patients' self-assessments using the VAS, the degree of pain relief was excellent/good in 72 of 88 patients (82%). At the end of the follow-up period, 50% of the patients were in a better psychological status and 86% of the patients reported an improvement in activities of their daily living and a reduction in the use of analgesic medication. Ninety percent of the patients stated that they would go through the procedure again for the same result.

The findings of the present study indicate that spinal cord stimulation is an efficacious therapy for the treatment of chronic non-malignant pain.

Keywords: Neuromodulation; spinal cord stimulation; SCS; non-malignant pain; chronic pain.

Introduction

In the treatment of chronic non-malignant pain, the first step is to verify that all anatomical causes that could be responsible for the pain were eliminated, corrected or repaired. If any possible anatomical correction was done and all available medical treatments according to the WHO-scheme and all physical therapies were tried without success, then spinal cord stimulation (SCS) can be considered. Treatment strategies for chronic non-malignant pain should follow the principle that less invasive and less costly interventions have to be preferred over invasive and costly treatments.

In 1967, direct electrical spinal cord stimulation was performed for the first time [19, 20]. Shealy used a single electrode placed in the subdural space. Earlier spinal stimulation electrodes required laminectomy or laminotomy for implantation under direct vision. In 1975, electrodes were implanted percutaneously. Almost all users now prefer percutaneous electrodes. One reason for this is that laminotomy is more traumatic and that the correct position of the electrode is determined by intraoperative stimulation in the wakeful patient during implantation under local anesthesia [7]. Currently percutaneously implantable electrodes are placed in the epidural space, and low-frequency electrical current is used to modify the transmission of chronic pain signals in the dorsal columns of the spinal cord.

In 1977, we reported the first application and results using this method [10].

Spinal cord stimulation evolved as a direct clinical application of the gate control theory, which was proposed by Melzack and Wall in 1965 [14]. The gate theory postulates a gate in the dorsal horn of the spinal cord that could be closed by activation of large afferent fibers or by activation of inhibitory pathways. SCS was thought to be effective in closing this gate. The exact mechanism of SCS is still unknown. Lately, experimental studies have shown that neuronal transmitters are involved in this mechanism and influence closing of the gate [3, 23].

Before definitive implantation of the SCS system, all patients undergo psychological screening and trial stimulation by temporary electrode placement.

After implantation of the electrodes, the trial leads are externalized and connected to the trial stimulator. The trial period ranges from 3 days to 3 weeks. Criteria for a successful trial include at least pain relief of 50%, reduced consumption of pain medications and increased

activities of daily living. The test pulse generator can be activated or deactivated by the patient, allowing the patient to become familiar with the basic control of amplitude and the sensation of paresthesia. The sensation of paresthesia should correspond with the area of pain. Throughout the test phase, a pain diary should be kept, in which pain intensity is recorded at least 3 times per day according to the Visual Analog Scale (VAS).

When a pain reduction measuring at least 50% according to the VAS is documented, the indication for a definitive implantation of the pulse generator is confirmed (Fig. 1).

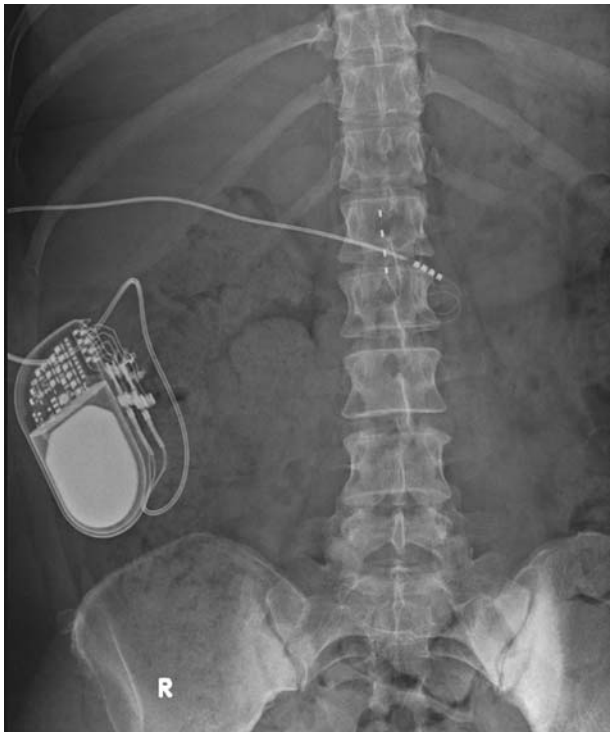

Fig. 1. Implanted pulse generator and electrodes positioned at level L1/L2

In the literature as well as according to our own experience, this temporary percutaneous trial is effective in approximately 90% of patients [11, 17, 21].

Equipment and configurations

SCS systems typically consist of three components designed to work together: leads, generator or receiver, and programmer or transmitter.

Leads

Leads are very thin wires or cables. One end of the lead is connected to the implanted generator or receiver, and the other is placed near the dorsal column that is going to be stimulated. The end of the lead that is positioned at the dorsal column has metal electrodes that can deliver mild electrical impulses. Leads can vary in type according to the implantation procedure (percutaneous or surgical), number of electrodes [4, 8 or 16], electrode shape, configuration, spacing and length (Fig. 2). Percutaneous leads can be implanted through a needle without surgical incision in a fluoroscopic room. The disadvantages of percutaneous leads include a) the risk of position changing, and b) the fact that their cylindrical electrode shape makes them less energy efficient. The advantages of surgical leads, also called paddle-leads, are: a) a decreased risk of position changes, and b) the fact that their flat shape makes them more energy efficient. However, they require a laminectomy or laminotomy surgical procedure. Percutaneous leads are always used for test stimulation, whereas for permanent implantation either percutaneous or surgical leads can be used.

The commercial lead has 4–16 electrodes. The number of electrodes used depends on the condition to be treated as well as the physician's preference. Patients

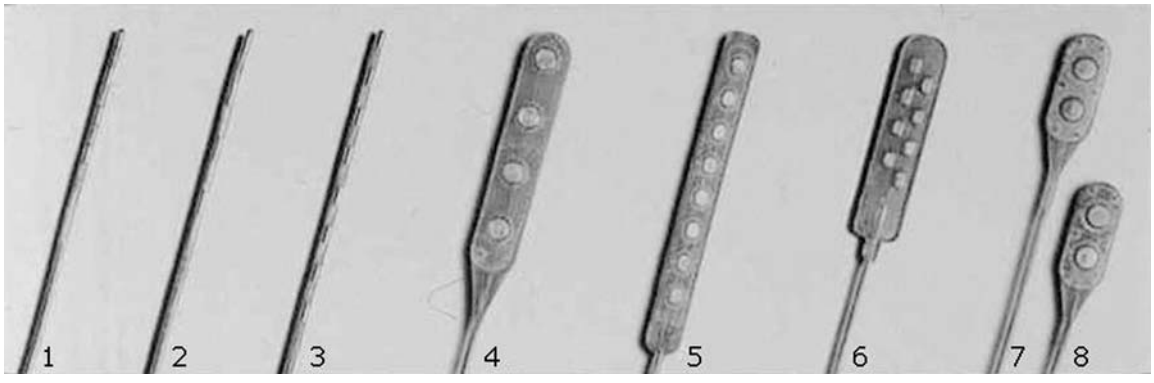

Fig. 2. Spinal cord stimulation electrodes are usually placed percutaneously through a Tuohy needle (*1–3*), paddle-leads require laminectomy or laminotomy (*4–8*)

with complex pain patterns, with more than one area involved or with bilateral pain in both extremities, need complex electrode configurations and implantation of larger paddle-leads. In fact, many physicians prefer to implant additional electrodes, in case the pain pattern changes or the lead migrates. If a change or migration occurs and additional electrodes are available, pain relief can be re-established by electronically repositioning the stimulating electrodes.

Power source

Three types of SCS systems are available for spinal cord stimulation: conventional implantable pulse generators, rechargeable implantable pulse generators, and radio frequency systems. Each of these systems uses a different power source to transmit electrical energy to the electrodes. The conventional implantable pulse generator is powered by a battery. The pulse generator itself consists of the battery and electronics that are housed in a single metal container, which is completely implanted under the skin. When its battery runs out, the pulse generator must be surgically replaced. The rechargeable implantable pulse generator has to be changed and replaced surgically too, but the batteries are rechargeable. The radio frequency system is a telemetric system. A receiver is implanted under the skin and the transmitter is placed externally on a belt. In this system no battery is used and energy is telemetrically transmitted from outside (Fig. 3).

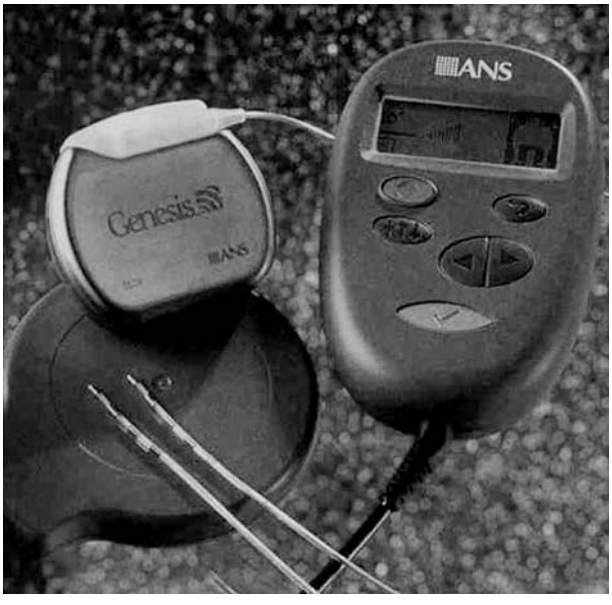

Fig. 3. Telemetric SCS system with electrodes, the receiver implanted under the skin, the transmitter placed externally on a belt and programmer

Programmer or transmitter

Programmer or transmitter is a device used to program the SCS system and adjusts the intensity of the stimulation. Programs include various electrical settings (amplitude, frequency, pulse width, and polarity) transmitted to each electrode on the lead. The external programmer or transmitter allows creating as many programs as the patient feels necessary to control his/her particular pain pattern. Programs can be changed and stimulation can be regulated up or down by remote control.

Indications for SCS

A specific diagnosis should be established as an objective basis for further treatment of pain. There should be neither abnormalities on diagnostic imaging exams nor objective physical/neurological findings consistent with the patients' pattern of pain. Spinal cord stimulation should be undertaken as late or last resort after alternative treatments have been exhausted. For failed back surgery syndrome, other surgical options should be considered although conventional re-operations in many cases carry a greater risk. Multidisciplinary evaluation of the patient is important, particularly psychological evaluation. Relief of pain should be demonstrated by placement of a temporary electrode and trial stimulation before a permanent pulse generator is implanted. During this phase it should be ascertained that the pain area is overlapped by paresthesias as induced by the stimulation system [12, 16].

Over the last four decades, the following conditions have been treated successfully with implanted spinal cord stimulators:

1. The most common indication for spinal cord stimulation is failed back surgery syndrome. These patients commonly have axial low back pain associated with pain in the lower extremities [2, 4, 9, 15, 22, 25].

   In many cases, axial low back pain may be nociceptive or mechanical, and this kind of pain does not respond as well to SCS as neuropathic or deafferentation pain [24]. Patients with unilateral lower extremity pain are more easily treated than those with bilateral pain.
2. In recent years, ischemic pain associated with peripheral vascular disease in the lower extremities has become the most common indication for application of spinal cord stimulation [8, 18].
3. Peripheral nerve injury, neuropathia or neuralgia, causalgia, and reflex sympathetic dystrophy also respond to spinal cord stimulation [6].

4. Postamputation pain syndromes including phantom limb and stump pain in most cases respond to spinal cord stimulation [21].
5. Further applications of spinal cord stimulation for pain include management of spinal cord injury, angina pectoris and management of intractable pain associated with severe spasticity of the lower extremity [5, 13]. In this clinical condition, a combination therapy including SCS and intrathecal drug delivery may be necessary [3].

In general, results are much better in patients with a more peripheral distribution of pain. Unilateral pain in the extremities will very well respond to stimulation. It is possible to treat pain in both extremities with the aid of dual systems and by multiple electrodes.

Clinic material and methods

In the last 7 years, from January 1999 to 2005, 145 patients were treated with an SCS system for chronic non-malignant pain in our clinic. Our retrospective analysis is based on data derived from 88 patients with chronic non-malignant pain. Follow-up in our study ranged from 15 to 75 months, with a mean of 60 months. Mean age was 45 years with 55% of the group being male. The main duration of pain history was 8 years.

Indications in these 88 patients were mainly neuropathic pain syndromes, like postdiscotomy syndrome (33 patients), posttraumatic pain (23 patients), reflex sympatatic dystrophy (10 patients), phantom limb pain (7 patients), stump pain (6 patients), low back pain (3 patients), posttraumatic intercostal neuralgia and polyneuropathia (4 patients). All patients underwent temporary trial of SCS. These 88 patients fulfilled the criteria of implantation of a permanent SCS system.

Patients were evaluated according to the Visual Analog Scale (VAS), level of activity and subjective assessment of the quality of life. Pain relief was rated good if pain reduction was at least more than 50% and excellent if pain reduction was over 70%.

The implantation of SCS was performed under local anesthesia to allow the patient and the surgeon to communicate during the perioperative test stimulation.

Patients were in a prone or in a sitting position on a radiolucent table. The percutaneous electrodes with 4 or 8 stimulation contacts were placed percutaneously in the epidural space through a Tuohy needle under fluoroscopic control at the appropriate level, as determined by patient paresthesia. Paresthesias induced by the stimulator should correspond to the area of pain.

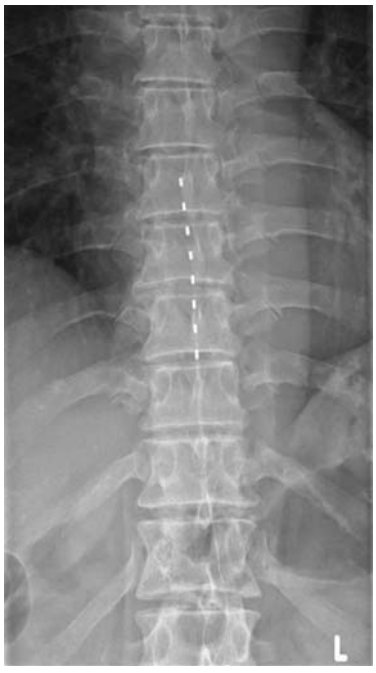

Fig. 4. Percutaneously implanted octopolar lead at levels Th 7, Th 8 and Th 9 in a patient with low back pain and radiculopathy

When the tip of the electrode is in correct position, the lead is fixed and connected externally to a pulse generator. Patients with low back pain for instance have typical electrode positions at level Th 9 and Th 10 intervertebral disc spaces (Fig. 4). When the first lead has been tested, the second lead may be placed parallel in the radiological midline of the spine. The trial leads are externalized through a subcutaneous tunnel and connected to the trial stimulator. The parameters of the stimulation signal are: amplitude 3–10 mA, frequency 30/80 Hz, pulse width 60–450 µsec.

Before permanent implantation, efficacy of the spinal cord stimulation was evaluated during the test phase to determine its analgesic effect and tolerability. The test pulse generator could be activated or deactivated by the patient allowing the patient to become familiar with the basic control of the amplitude and the sensation of paresthesia. The patient was discharged the day after implantation under oral antibiotics. Throughout the test-phase, between 10 and 21 days, a pain diary was kept, in which pain intensity was recorded at least 3 times daily according to the VAS. When pain reduction of at least 50% according to the VAS was reached, the indication for definitive implantation of the pulse generator was confirmed. The pulse generator then was generally placed in a subcutaneous pocket in the upper abdominal wall.

Clinical results

Self-assessment of these 88 patients provided the following results (mean follow-up 60 months). Preoperatively all patients had shown a VAS score over 6. Based on the patients' self-assessment using the VAS, the degree of pain relief at last follow-up was rated excellent in 32 patients (36%), good in 40 (45%), and moderate or poor in 16 (19%).

Prior to treatment, 82 of the 88 patients had described themselves as being not energetic or withdrawn and had social problems due to intense pain. At the end of follow-up, only 35 of the 88 patients still considered themselves as being passive or withdrawn, which means 40% compared to 92%.

Seventy-six of 88 patients (86%) reported an improvement in activities of daily living and a reduction in the use of analgesic medication. Seventy-nine of 88 patients (90%) stated that they would go through the procedure again for the same result.

In our series, there was no major morbidity with regard to spinal cord stimulation. The overall rate of wound infections was 6%. All wounds healed promptly after removal of the leads of the pulse generator and a short course of antibiotics, thus allowing a second implantation. The only technical problems we encountered were dislocation of the electrodes or the pulse generator in very few cases. In all patients, these problems were corrected surgically.

Conclusions

Over the past 4 decades, techniques and devices for spinal cord stimulation have undergone considerable refinement. The earliest devices required a laminectomy or laminotomy for placing an intraspinal monopolar of bipolar electrode. With increasing experience and recognition of the importance of proper electrode placement, percutaneous methods were being developed for insertion of temporary trial screening electrodes. Very soon, these evolved into percutaneous methods for the implantation of permanent electrodes. Correct placement of the stimulation electrode in the dorsal epidural space is of critical importance for the success of the procedure as can be proved by test stimulation. In our series, after trial, 90% of patients received permanent implants.

Implantation of the temporary trial electrodes should be performed under local anaesthesia; this allows the patient and the surgeon to communicate. Paresthesias induced by the stimulator should correspond to the area of pain, if the tip of the electrode is in correct position.

Success of SCS is also dependent on the selection of patients, which should be based on extensive interdisciplinary examinations including psychological evaluation and after extensive use of more conventional therapies.

The results of the present study indicate that spinal cord stimulation is an efficacious, comfortable and safe therapy for the treatment of non-malignant, particularly neuropathic pain syndromes. Moreover, SCS is a cost effective treatment given that it improves the quality of life and employment prospects, allowing a relatively high rate of return to work [1, 8, 17].

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Dual electrode spinal cord stimulation in chronic leg and back pain

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Summary

Patients with chronic back and leg pain (CBLP) suffer from a disabling spinal condition of multifactorial origin and are often resistant to medical therapy. Spinal cord stimulation (SCS) is a minimally invasive option for treatment of chronic pain in these patients, which involves placement of epidural electrodes close to the midline of the spinal cord. SCS was originally introduced and used for decades with a single electrode. The development of fully implantable dual channel pulse generators connected to dual multicontact electrodes has given pain clinicians a more versatile tool to treat axial low back pain accompanied by radicular neuropathic pain with irregular and asymmetric distribution, a feature which is found in most CBLP patients. It has been hypothesized that using dual electrodes may improve long term outcome for CBLP patients compared with single electrodes. Current evidence however does not lend strong support to this assumption. Given the high cost of treatments for CBLP and of SCS itself, there is an urgent need for high-quality evidence for the effectiveness of dual electrode SCS in relieving pain and/or improving function in patients with CBLP.

Keywords: Chronic back and leg pain; CBLP; spinal cord stimulation.

Introduction

Chronic pain of benign origin is a widespread but underestimated cause of physical and emotional distress to individuals and financial losses to society. One of the modalities available since the 1960s for treatment of chronic pain refractory to medical and physical therapy is spinal cord stimulation (SCS), a minimally invasive surgical method where weak pulses of electricity are applied in a controlled fashion close to the dorsal surface of the spinal cord [9, 24]. The mode of action of SCS is based on the gate-control theory [10]. After initial delay due to insufficiently advanced technology and less suitable indications, the method of SCS has achieved widespread clinical acceptance and recognition the last two decades [1, 2]. The introduction of routine single percutaneous electrode implantation in the early 1990s made possible the minimally invasive trial stimulation, which is now thought to be an indispensable step in the selection of patients with maximum benefit from SCS [7, 15, 22].

SCS has become a viable therapeutic option for patients suffering from chronic benign pain resistant to any other standard treatment. The sympatholytic effect of SCS is the most obvious of its therapeutic properties [14, 23]. It seems that SCS abolishes continuous and evoked pain (in particular allodynia), while acute nociceptive pain such as wound pain, arthritis or ischaemic heart pain is unaffected. The precise mechanisms of action of SCS are however still insufficiently understood [7].

Patients with chronic back and leg pain (CBLP) suffer from a disabling spinal condition of multifactorial origin and are mostly resistant to medical pain therapy [3, 16, 18]. The term CBLP describes a heterogeneous pool of presumably different pathogenetic mechanisms leading to a common set of symptoms. CBLP patients have long clinical histories and require systematic follow-up because the severity of their condition may vary considerably over time. SCS with a single multipolar electrode has shown efficacy in CBLP patients, however it emerged in some cohorts that the radicular neuropathic component of CBLP may be better influenced by SCS than the axial low back pain (nociceptive pain) component [7, 13, 23]. Many clinicians use SCS to treat predominantly radicular rather than axial low back pain because of the technical difficulty in achieving coverage by paresthesia of axial low back pain with single electrode SCS systems [1].

The development of fully implantable dual channel pulse generators connected to dual multicontact electrodes has allowed pain clinicians to treat axial low back

pain accompanied by radicular neuropathic pain with irregular and asymmetric distribution, which is found in most CBLP patients. It has been hypothesized that using dual electrodes and increasing the number of contacts may improve outcome for CBLP patients [11, 13]. There is an urgent and largely unmet need for high-quality evidence regarding the effectiveness of SCS in relieving pain and improving function.

This review summarizes the personal experience of the authors and reviews the available evidence for efficacy of dual electrode SCS systems in CBLP treatment.

Chronic back and leg pain (CBLP) syndrome

The so-called failed back surgery syndrome (FBSS) is common throughout the Western world and especially in the United States because of the high numbers of surgical procedures for low back and leg pain [4]. Treatments for this heterogeneous pain condition are varied, mostly unproven by evidence, and often rather costly [18]. CBLP is often used synonymously with FBSS, although unlike FBSS, CBLP may arise without prior surgery. CBLP represents a complex chronic pain syndrome usually defined by its anatomical localization in the lumbar spine and lower extremities. It is of multifactorial genesis and may be the consequence of various lumbar spinal diseases, including arachnoiditis, degenerative disc disease, epidural fibrosis, lumbar disc herniation, osteoporosis, or spinal canal stenosis [16]. Pain patterns in CBLP may include neuropathic components, but the main feature is usually nociceptive pain. Although degenerative or postsurgical disc pathology is thought to be a common cause of CBLP, the relationship between the extent of disc damage and the degree of clinical symptoms is not clear. A strictly mechanical or anatomical explanation for CBLP has proved inadequate [21]. Transition from acute to chronic low back and leg pain is further influenced by psychological and social factors [3, 17].

Rationale for dual electrode spinal cord stimulation for CBLP

Despite the scarcity of published evidence, it seems universally accepted that SCS is clinically beneficial in patients with radicular neuropathic pain [1, 7, 14]. Most patients with CBLP however have a mixed pain pattern with neuropathic and nociceptive components and, in addition to the axial low back pain, scattered painful dermatomes over both buttocks and legs. It has been generally accepted that a single percutaneous electrode with 4 contacts cannot sufficiently cover pain in the midline and in bilateral dermatomes and therefore paresthesia, which is seen as the best prognostic indicator for pain relief by SCS, cannot be distributed evenly to cover all painful areas in the axial and lateral areas of the body [5, 13]. Dual electrode systems with 4 or 8 contacts each have been developed with the notion that two electrodes can be positioned close to the midline on each side, and that extended contact coverage in the lateral and cephalad-caudad planes will allow for generation of paresthesia in every necessary dermatome [20]. Separate programming of each electrode and of each contact has resulted in an almost unlimited numbers of combinations of the contacts on each electrode and between the pairs, which in turn demonstrated the necessity of some kind of computerized algorithm for selection of the most efficacious combinations [15].

Evidence for efficacy of SCS for CBLP

Single electrode SCS

An early systematic review of SCS for CBLP found the methodological quality of the then existing literature to be poor [24]. The lack of randomized trials precluded conclusions regarding the effectiveness of SCS relative to other treatments, placebo, or no treatment at all. Turner *et al.* have recently published an updated review to include data from new studies [25]. The authors concluded that still more methodologically robust studies are needed to establish the effectiveness of SCS, although a few randomized controlled trials (RCT) were carried out in the last decade.

Mailis-Gagnon *et al.* conducted the first systematic Cochrane review of SCS for chronic benign pain [9]. Only one RCT fulfilled the inclusion criteria of the review and the authors concluded that currently there is insufficient evidence to determine the benefits and adverse effects of SCS [13]. In the RCT included in the Cochrane review, North *et al.* investigated SCS for lumbosacral radicular pain [14]. The authors reported that after 6 months therapy 17% (2/12) of SCS patients requested cross-over to back surgery in comparison to 67% (10/15) of the control group undergone surgery who sought cross-over to SCS. Another more recent RCT from the same group proved that in patients with persistent radicular pain SCS is significantly more effective than reoperation and in the great majority of patients obviates the need for reoperation [12].

In the virtual absence of RCT evidence, it is worth noting some lower class evidence from other studies. In a large prospective multicenter study, only 70 of 182 CBLP patients who received a permanent SCS implant (single percutaneous electrode or surgical plate electrode) completed the follow-up [2]. One-year follow-up data showed statistically significant improvement in measures of pain and quality of life, but not in medication use or work status. Dario *et al.* reported a study of SCS in CBLP. Twenty patients responded to medical treatment (medical group), 23 patients did not respond to medical treatment and received permanent SCS implants. Mean follow-up was 42 months. In terms of mean values for leg and back pain and for disability, the medical treatment group improved significantly more than the SCS group [5]. Kumar *et al.* treated 60 CBLP patients with permanently implanted SCS systems, 44 further cases failed trial SCS and were treated medically. At 5 year follow up, the SCS group improved by 27% and non-SCS group improved by 12% on disability measure, and 15% of the SCS group and none of the non-SCS group returned to work. However patient selection in this study may be biased by the non-random character of groups [8].

Dual electrode SCS

Devulder *et al.* used a device consisting of two multicontact electrodes connected to a radiofrequency-coupled system (Mattrix®, Medronic, Inc., Minneapolis, MN, USA) to treat two patients with CBLP. The authors stated that dual channel stimulation helped steering better stimulation paresthesias. They claimed that better distribution of stimulation-induced paresthesias was achieved in the back and the legs, however the case reports allowed for descriptive evidence only [6].

North *et al.* published a prospective controlled clinical trial comparing single and dual percutaneous electrodes in the treatment of axial low back pain. The authors hypothesized that placing two parallel electrodes would improve outcome. Twenty patients who passed screening with single percutaneous electrodes received permanent dual electrodes at the same vertebral levels. Patients acted as their own controls in evaluating the effects of single versus dual electrodes. The authors found that single electrodes provided significant advantages ($p < 0.01$) in pain coverage by paresthesias compared with the same electrodes implanted as a pair. Amplitude requirements were significantly lower for the single electrode than for either dual electrode. A total of 53% of patients with dual electrodes nevertheless met the criteria for long-term clinical success. The authors concluded that there are some disadvantages for dual electrodes in treating axial low back pain [13].

Rutten *et al.* examined the effects of dual electrodes (8 contacts each) in patients with postsurgical CBLP. Thirty-four patients received permanent implants. Dual electrode systems were implanted in 23 patients and single electrode systems in 11 patients. Follow-up was 24 months. The authors reported paresthetic coverage of painful areas in all patients, which remained constant over the whole follow-up period. All measurement scales confirmed reduction of pain and improved quality of life as a result of SCS, irrespective of the number of electrodes. No further comparisons were however reported between the dual electrode and single electrode groups [20].

Personal experience with dual electrode SCS systems

The authors have used dual electrode/dual channel SCS systems in their clinical practice since 1997. Various hardware configurations and systems (ANS, Inc.; Medtronic, Inc.) were used in combination with percutaneous dual electrodes with 4 or 8 contacts each. Initially, a radiofrequency-coupled dual channel system (Mattrix®, Medtronic, Inc.) was used with standard 4-contact electrodes (Pisces Quad®, Medtronic, Inc.) to treat patients with CBLP who had bilateral leg pain combined with axial low back pain. We found that dual electrode stimulation using the Single Stim™ technology (same amplitude and pulse width on both electrodes with at least one cathode and one anode on either electrode) significantly increased the ability of the SCS system to cover painful areas with precisely placed stimulation-induced paresthesias. Placement of the electrodes was parallel to each other on both sides of the physiological (not anatomical) midline and covering the same vertebral segments in the cephalad-caudad direction. With this system we were able to achieve better paresthesia coverage in the back and at the same time in various dermatomes in both legs, however the radiofrequency system with external pulse generator was inconvenient for the patients and a few became allergic to the material of the antenna.

With the advent of fully implantable dual channel pulse generators (Synergy®, Medtronic, Inc.) we started using those instead of the radiofrequency systems for the same indications. Additional programming capability of

the software (DualStim™ mode with different amplitudes and pulse widths on both electrodes) allowed for further increase in the possible contact combinations and for the usage of dual electrodes placed close to the midline with their contacts covering two spinal segments instead of one. This we found helpful when there were thoracic and sacral dermatomes affected at the same time. In general, our clinical practice has shown that the cathodes (−) on each electrode should be localized ipsilateral or median to the painful sides, proximal to the most proximal pain dermatomes, and flanked by two anodes (guarded cathode). After more than 20 CBLP patients implanted with dual electrode systems, our experience confirms that dual electrodes actually shorten the duration of the test implantation procedure because their greater paresthetic coverage is more forgiving and only calls for approximate intraoperative placement. This in turn considerably shortens intraoperative test times and reduces the need of X-ray fluorography in the operating theatre, compared to single electrodes. Further advantages of the dual electrode system are significantly better ability to cover irregular pain patterns and capacity of almost unlimited programming combinations of channels and contacts. On the other hand, dual electrodes have higher energy requirements and reduce battery life of the implanted pulse generator.

We have not seen increased rates of hardware failure with dual electrode systems compared with single electrode ones. Although a prospective comparative analysis has not been carried out yet, we did investigate a cohort of 42 CBLP patients with long term single electrode SCS (6 to 74 months duration). Twelve surgical corrections of the hardware were carried out in a total of 10 patients over the assessment period. In 8 patients there was a single corrective procedure, in 2 additional cases there were two surgically corrected hardware failures each. The most often encountered type of hardware failure was electrode breakage or disruption of insulation (in Pisces Quad® percutaneous electrodes only) leading to short-circuiting and dysfunction ($n = 8$). Second in frequency were failures due to insulation leakage at the pulse generator plug connection site ($n = 2$). In one further case, extension cable breakage caused dysfunction of the system, and another dysfunction was caused by distal extension cable disconnection [19].

There is no evidence from our clinical practice and in the published literature to suggest that dual electrode SCS results in a significantly increased rate of complications or side effects [13, 20]. However reported complication rates for single and dual electrode systems vary widely across studies, and differences in patients. SCS equipment, clinical settings, complication assessment and reporting, length of follow-up and other factors may strongly influence the reported numbers of complications [23–25]. According to Turner *et al.*, the median percentages of complications from single electrode SCS were as follows: superficial infection 4% (range 0–12%), hardware failures 6.5% (range 0–40%), pulse generator revision (additional operation) for reasons other than battery change 21.5% (range 0–81%), pulse generator removal 6% (range 0–47%). Sample sizes in the reviewed studies were however small and lengths of follow-up and reported complication rates were highly variable [25].

Conclusions

At the present time there is little high-class evidence that SCS is effective for chronic benign pain, although clinical practice confirms its efficacy and safety. Most published trials are retrospective case collections and use single electrode SCS for radicular neuropathic pain. Only a few published trials deal with dual electrode SCS for axial low back pain and CBLP. There is a clear need for large scale RCT to evaluate SCS in comparison to other standard therapies for CBLP. There is also a need to evaluate different hardware configurations for SCS in homogeneous patient groups and with unified criteria.

Based on our own experience and on a comprehensive review of the current literature, we conclude that evidence is inadequate to make definitive statements about the difference in efficacy of dual electrode systems compared to single electrode SCS. However it should be noted that dual electrode SCS has considerable practical advantages in CBLP cases and that hardware complication rates seem to be comparable to those of single electrode SCS.

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Factors affecting spinal cord stimulation outcome in chronic benign pain with suggestions to improve success rate

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Summary

For patient selection, psychological factors like fear avoidance, depression, secondary gain or refusal to be weaned off narcotics should be avoided. Trial Stimulation is an important tool to reduce the rate of failed permanent implants, and to improve cost-effectiveness. The etiology of pain has a strong influence on the success rate. The success rate is inversely proportional to the time interval from the initial onset of symptoms to the time of implantation. Multi-polar and multi-channel systems improve the long-term reliability and success rate and have proven to reduce the incidence of open surgery in case of electrode displacement. Third party coverage like the Worker's Compensation negatively affects the long term success. Reducing the complication rate directly benefits long term success rates. The electrode fracture rate can be reduced by using the paramedian approach, the use of three wing silicone anchor placed immediately at the point of exit of the lead from the deep fascia and avoiding a hard plastic twist lock anchor. The displacements can be reduced by fixing the anchor to the deep fascia firmly, supplemented by the use of silicone glue, and by placing the implantable pulse generator (IPG) in the abdominal wall, instead of the gluteal region. The use of prophylactic antibiotics tends to reduce the infection rate.

Keywords: Spinal cord stimulation; complications; chronic benign pain; long-term success rate.

Introduction

Chronic pain is a pervasive medical dilemma with complex physiological and psychological origins that have yet to be fully elucidated. Chronic pain poses a social, economic and emotional burden for those afflicted and for society as a whole. This results in depression, poor quality of life and ultimately loss of livelihood. Pain is the major driving force for a patient to seek medical attention. Spinal Cord Stimulation (SCS) in the treatment of chronic pain has become an established modality since its introduction in 1967 by Shealy *et al.* [25]. Melzack and Wall, by propagating the gate theory, stimulated new interest in pain research and therapy [19]. However the gate theory does not fully explain the mechanism of SCS pain control, as stimulation does more than directly inhibit pain transmission in the dorsal horn of the spinal cord. Pain modulation by SCS may also involve supra-spinal activity via the posterior columns of the spinal cord, probably by recruiting endogenous inhibitory pathways. Our improved understanding of the neurotransmiter systems, for example GABA and adenosine, will help to unlock this mystery.

Since 1967, SCS has been steadily gaining support as a reversible and non-destructive method of effectively controlling chronic intractable pain. It has been shown to be efficacious in Failed Back Syndrome, Complex Regional Pain Syndrome I and II, Peripheral Vascular Disease causing rest and claudication pain, Multiple Sclerosis, Intractable Angina, Peripheral neuropathy, Postherpetic neuralgia and recently in certain cases of visceral pain [3–9, 14]. It is estimated that, in 2004, over 25,000 SCS systems were sold worldwide with total sales expected to rise each year. With the acceptance and proliferation of this technique it is important to investigate how factors like patient selection, various pathologies responsible for chronic pain, technological and methodological related factors and complications influence patient outcomes. We plan to reflect on our experience of the last 25 years in treating chronic pain with SCS to shed some light on these questions. The authors hope that the suggestions put forward in this study will be useful to improve the overall long-term success of this therapy.

Methods

To determine the factors affecting the long-term success in the treatment of chronic pain by SCS we undertook a retrospective in-depth

analysis of our active database of 424 patients spread over a 23 year period, with a mean follow-up of 97.6 months. Our study group consisted of 259 males and 165 females, with a mean age of 54 years and a range of 21–87 years. In this study we had early success rate of 80% (338 patients) and a long term success rate of 74.1% of the internalized group (251 patients), or 59.2% of the total study group patients. The analysis was focused on the value of trial stimulation and clinical predictors of outcome including age, sex, etiology of pain, type of electrode used, duration of symptoms prior to SCS implantation, number of surgeries prior to SCS implantation, effect of third party coverage and psychological factors.

We examined the causes of long-term failures and identified a group of 85 patients, who, after an initial period of good pain relief, start to require increasing amplitude of current to maintain satisfactory pain control. Over time, these patients' pain control eventually fades despite a fully functional stimulating system. For lack of better terminology, we have labeled this phenomenon as "tolerance".

Complications were analyzed as they influenced the long-term effectiveness of this treatment modality. We have included practical suggestions of how to minimize the occurrence of complications which is supported by recent bench data, supplied by Medtronic's neuro technology design engineering laboratories in Minneapolis, Minnesota. To achieve this bench data, the following methods were used by Medtronic Lab: 1) Computer modeling and anthropometric data provided understanding of the expected movement of the relevant anatomy. 2) Chronic animal studies provided estimation of the mechanical properties of tissues surrounding the implanted SCS systems. 3) A number of biomechanical tests were performed, to determine the loads on the lead, anchor and other parts of the system, to simulate conditions which lead to the types of complications recorded in this study (especially lead fracture and displacement) and to evaluate the best anchor.

Factors influencing the long term success

Patient selection

The proper patient selection has a major impact on the ultimate outcome and time spent in achieving this pays high dividends ultimately. For this purpose we suggest the patient should meet the following criteria: 1) a well defined, non malignant organic cause of pain 2) failed a trial period of initial medical pain management of roughly 6 months 3) remedial surgical procedure is not feasible or advisable 4) absence of secondary gain 5) absence of any major psychiatric disorder 6) willingness to eliminate any inappropriate drug use prior to implantation.

Role of trial stimulation

In spite of our effort in selecting appropriate candidates for SCS therapy, 17–20% of patients fail trial stimulation. This emphasizes the role of trial stimulation as it tends to reduce the rate of failed permanent implants and improves cost-effectiveness. The trial stimulation provides a window for the patient to adjust to the stimulation induced paraesthesia and counseling by a neurosurgical team. In our experience, the stimulation induced paraesthesia should cover a minimum of 80% of the area of the pain (if not the whole territory); otherwise the results are less than optimal. However, recently Allergi *et al.* [2], in their study have shown that complete coverage is not necessary to achieve good outcome. The main disadvantage to trial stimulation is an added procedure and associated costs.

The reason for failure of trial stimulation in patients who are otherwise considered good candidates for SCS is not understood at this time. It is postulated that this group may be an example of patients whose primary pain mechanisms or pathology are poorly suited for SCS, or whose anatomy or physiology is some way may prevent accurate electrode placement.

Table 1. *Etiology of pain, internalization, and long-term success rates*

Etiology	No. of patients	Initial pain relief		Long term pain relief	
		Success	Failure (not internalized)	Long term successes (%)	Late failures
FBSS	227	189	38	136 (60%)	52
Peripheral vascular disease	52	42	10	32 (62%)	10
CRPS I and II	34	29	5	25 (74%)	5
Peripheral neuropathy	20	16	4	14 (70%)	2
Phantom limb pain/stump pain	5	1	4	1 (20%)	0
Multiple sclerosis	19	17	2	15 (79%)	2
Angina	11	11	0	9 (100%)	0
Bone and joint pain syndromes	8	8	0	3 (37%)	5
Spinal cord injury/lesion/cauda equina syndrome/paraplegic pain	15	7	8	5 (33%)	2
Perirectal pain	6	4	2	3 (50%)	1
Post-herpetic/intercostal neuralgia	19	10	9	4 (21%)	6
Upper limb pain secondary to disc surgery and miscellaneous pain syndromes	8	4	4	4 (50%)	0
Total	424	338	86	251 (59.2%)	85

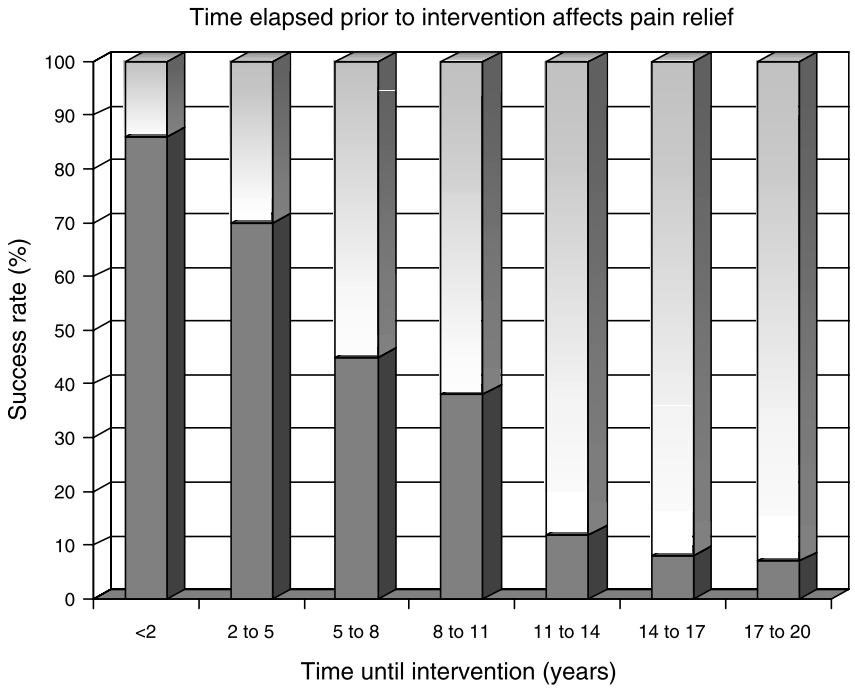

Fig. 1. The rate of success of SCS is inversely related to the time interval between the beginning of the chronic pain syndrome and the time of implantation. The success rate decreases from 85% with a delay of less than 2 years to approximately 8% if the delay is 15 years or greater. □ Failure, ■ success

Etiologies

In our experience the etiology of the pain is a crucial factor in predicting outcome, with success rate varying depending on the etiology treated. Our findings are consistent with other investigators. The most satisfying outcomes are achieved in Failed Back Surgery Syndrome (FBSS), CRPS I and II, peripheral vascular disease not amenable to revascularization surgery, refractory angina, peripheral neuropathy and pain secondary to multiple sclerosis [5, 10, 11, 13, 15, 16, 18, 20, 22, 23]. The treatment of refractory angina with SCS seems to give the most gratifying long-term success rate ranging from 90–100% [17, 18]. Less gratifying pain control was achieved in intercostal neuralgia, post-herpetic neuralgia and phantom limb pain, spinal cord injury, paraplegic pain, bone and joint pain syndromes, perirectal pain, and spinal cord tumors that progress to total paraplegia [16] (Table 1).

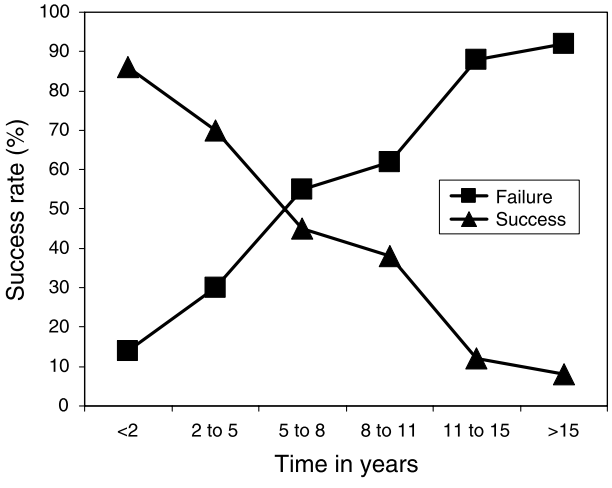

Fig. 2. Success and failure are plotted against the time of implantation. These lines intersect at 5 years, indicating that, to achieve best results, patients should be implanted prior to 5 years from the onset of their symptoms

Timing of implant

We have found that the success rate of SCS is inversely related to the time interval between the onset of chronic pain syndrome to the time of implantation. Figure 1 shows that the success rate decreases from approximately 85% for a delay less than 2 years, to approximately 8% if the delay is 15 years or greater ($p < 0.001$). On plotting the success and failure rates against the number years from onset of chronic pain symptoms to the time of implantation, the lines intersect at 5 years. This indicates that, to achieve the best results, patients should be implanted prior to 5 years from onset of their symptoms (Fig. 2). This may be due in part to reinforcement of pain pathways over time and subsequent learned behavior, making changes in these pathways more resistant to treatment with SCS with passage of time.

Pre-implant surgeries

In this series, 331 patients had one or more surgeries prior to consideration for SCS therapy (2.9 ± 1.3 aver-

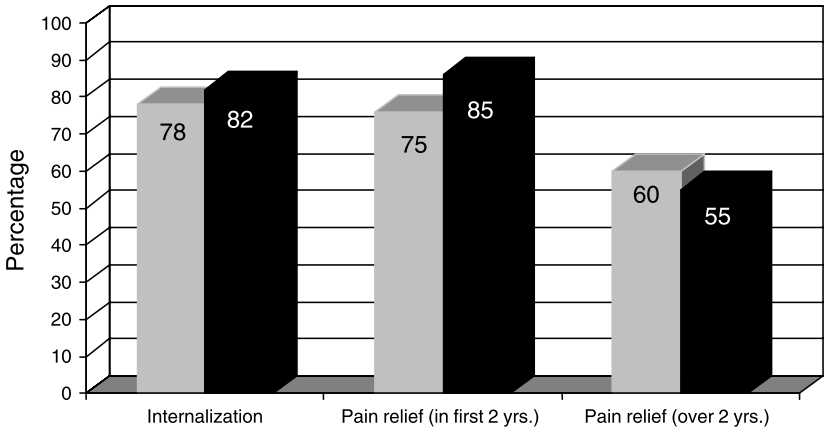

Fig. 3. Females have a slightly higher rate of internalization, and better pain relief in the first year, but over the long term, males experienced higher success rates. Male, female

age procedures [mean ± SD]). Among the 79 patients who had 3 or more surgeries 51% had long term success, as compared to a long term success rate of 53% for the 252 patients having less than 3 surgeries. The Fischer's exact test failed to show a statistically significant relationship between the two groups ($p = 0.69$).

Among the group of 39 patients who had no preimplant surgery comprised of patients with MS pain or peripheral neuropathies, the long-term success rate was 75%. This finding may be taken with the caveat that these represent entirely different disease processes as compared to patients who require surgical treatment for their underlying pathology.

Demographics and success rate

We have found no significant influence of age, gender or laterality of pain with respect to long-term success. Females in our series had a slightly higher rate of internalization and better pain relief in the first year. But, on long term follow-up males experienced a higher success rate (Fig. 3).

Influence of third party coverage

We have excluded patients from enrollment who were involved in active litigation or found to have unresolved issues of secondary gain. Worker's Compensation coverage is not subject to litigation by law in many countries including Canada, and acts as health insurance and disability benefit. Therefore, it was logical to consider the influence of WCB in propagation of long term disability in patients with FBSS who were subject to SCS. In our series 106 patients with FBSS with WCB coverage were enrolled. Of these, 89 (83.9%) had there systems internalized after a trial stimulation and at the last follow-up 54 (50.9%) continue to have good pain relief. On the other hand, of the 121 patients with FBSS without WCB coverage 95 (78.6%) had their systems internalized and 85 (70.1%) continued to have good pain relief at last follow-up. This is a statistically significant difference by Fisher's Exact Test ($p < 0.0038$).

Considering the return to employment following SCS 4 of the 89 (4.5%) internalized patients with WCB coverage returned to gainful employment as compared to 15 out of 95 (16%) internalized patients without WCB coverage returned to gainful employment. This difference is also statistically significant by Fisher's Exact Test ($p = 0.0387$).

This will indicate that Third Party Coverage negatively affects the success rate and return to employment. Even though we chose to exclude patients involved in active litigation, a recent study by Van Buyten *et al.* [29] reveals no difference in the VAS scores between patients involved in active litigation and the rest of the population.

Effect of electrode type on outcome

Our present and previous data [15, 16], supplemented by other investigators [20, 21], demonstrate that multi-polar and multi-channel electrode systems (hazard ratio = 0.47 $p < 0.001$, compared to unipolar system) are superior to achieve long-term successful pain relief. Plate electrodes have a slightly higher survival time than cylindrical multipolar percutaneously implanted electrodes (Fig. 4). The use of these systems also reduces the incidence of open surgery from 23% to 16% to restore paraesthesia coverage and pain relief after electrode displacement [21]. According to Alo *et al.* [1], only 3.8% cases required surgical revision with the use of octapolar leads and complex programming.

Lower extremity pain secondary to radiculopathy responds well to SCS, however when axial pain becomes more prominent it becomes difficult to treat. In the last

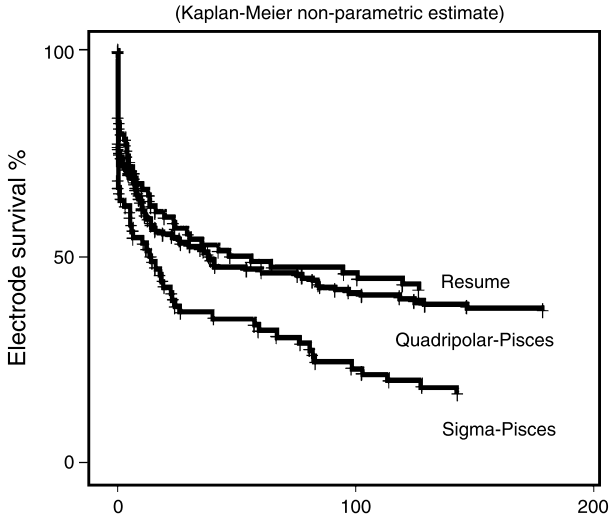

Fig. 4. Kaplan-Meier Survival Curve for the electrode types used in the spinal cord stimulation. The graph shows that plate type of electrodes have a longer survival time than Pisces type of electrodes. Reproduced with permission: Kumar *et al*. [16] Epidural spinal cord stimulation for treatment of chronic pain – some predictors of success. A fifteen year experience. Reproduced with permission Surg Neurol 50: 110–121

2–3 years we have been exploring various ways to control the axial pain as well. We have discovered that the dual quadripolar or dual octapolar leads, placed in a staggered fashion, seems to give a better control of axial pain. We attempted this approach to controlling predominant axial pain in 34 patients. At one year follow-up, the average reduction of axial pain on VAS was 58% with a reduction in radicular pain of 60%. In comparison, for 154 patients with FBSS with predominant leg pain and minor axial pain implanted with single lead systems, the reduction in the VAS score for the axial pain was 15% and the radicular pain 64%.

Effects of rapid cycling

Patients who show a decline in the effective pain control with conventional stimulation cycles can be salvaged by the introduction of rapid cycling which consists of "on" and "off" periods of 1 second or a fraction thereof. In 53 patients, where rapid cycling was tried there was an improvement in VAS score of 14 ± 6 points. Battery life can also be improved by rapid cycling but is confounded by other factors like pulse with and amplitude.

Effect of complications

Reducing the complication rate directly affects the long-term success rate. The complications not only disrupt the pain control effect, but also pose an additional expense to this treatment modality. The incidence of adverse events reported in the literature varies from 20–75% [26], with an average of 34–36% [9]. The complications

Table 2. *Complications*

Hardware complication	Incidence (%)	Comment
Displaced electrode	90 (21.23%)	42 were repositioned, 48 were replaced (49 of these displacements occurred in sigma electrodes). The displacement rate in sigma electrodes was 74.24% while in other types of electrodes is 9.5%
Fractured electrode	27 (6.37%)	All replaced satisfactorily; usual site was distal to the fixation point to the deep fascia where the lead enters the spinal canal
Hardware malfunction	20 (4.71%)	Due to increased impedance, electrodes were replaced
Insulation damage	9 (2.3%)	Occurred in cases where rigid twist lock anchor was used requiring replacement of the lead
Discomfort over pulse generator	27 (6.37%)	5 cases (1.2%) required revision In 2 cases, the pulse generator was placed too low in the anterior abdominal wall and caused irritation of the ilioinguinal nerve requiring repositioning In 2 cases, it was placed over the lower ribcage in the earlier part of the study and needed to be repositioned over the anterior abdominal wall In 1 case, when placed over the gluteal region the pulse generator caused pain on lying down, requiring repositioning The rest resolved with rest and conservative measures
90 Degree rotation of pulse generator	4 (0.94%)	Resulted from faulty anchoring of pulse generator to fascia, required repositioning
Electrical leak	4 (0.94%)	All were replaced. Usual site was junction of connector cord to distal electrode or pulse generator
Biological complications	*Rate*	*Comments*
CSF leak	2 (0.47%)	Resolved spontaneously
Subcutaneous hematoma	19 (4.48%)	At the site of the pulse generator; 1 required surgical evacuation, 8 required aspiration, and 10 resolved spontaneously
Infection	15 (3.5%)	Five resolved with antibiotics, ten required removal and subsequent re-implantation

that posed the largest threat to the long-term success rate in our series were: 1) displacement of the electrode, 2) fracturing of the electrode, and 3) infection (Table 2).

Electrode displacement

Electrode displacement can take place either in the vertical or horizontal plane depending on the direction of the forces on the lead. In the literature, the incidence of this complication was 13.2% [27]. In our series, the incidence of this complication was 9.5% if the sigma electrodes are excluded. The sigma electrode was the primary electrode in the early phase of the study, and was highly susceptible to displacement due to defective metallurgy. It had a single contact point, so even a slight displacement resulted in loss of pain control and undulations in its stem led to easy displacement by jerking or twisting of the back. The vertical migration may be caused by the lead slipping through the anchor, when tensile loads on the lead exceed the anchor's retention ability. It may also result when the anchor, which is secured to the lumbodorsal fascia, gets pulled away due to either failure of the suture holding it in place or due to the tearing away of the fascia. The tensile load on the lead changes with the motion of the spine, position of Intra-corporal Pulse Generator (IPG) and elasticity of the lead and the tissues. The length of excursion of the

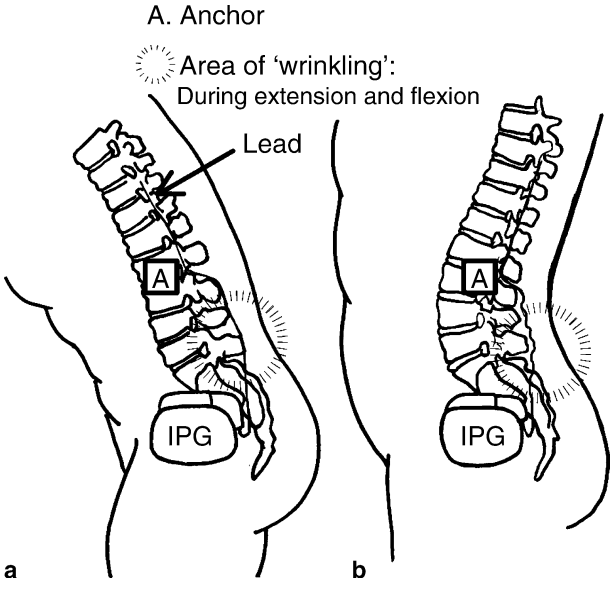

Fig. 5(a and b). Displacement of extension cord between neutral and extension position of the dorso-lumbar spine when IPG is in buttocks. There is displacement of 9 cm between anchor and IPG during neutral and extension of spine when IPG is in the buttock area (Bench data courtesy of Medtronic Inc.)

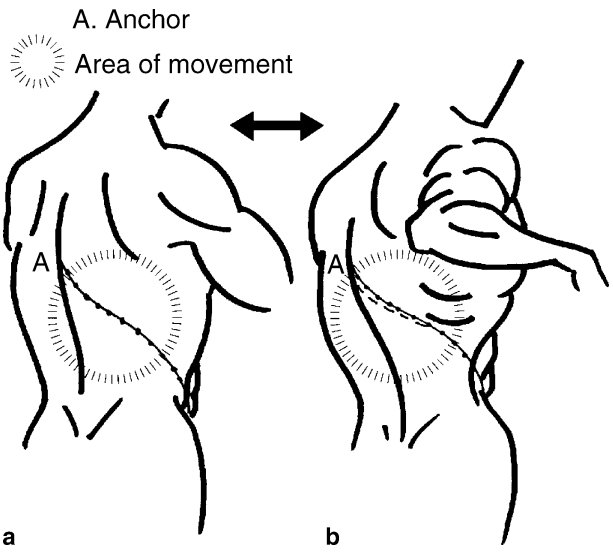

Fig. 6(a and b). Displacement when IPG is in the anterior abdominal wall. There is displacement of only 0.2 cm between anchor and IPG during walking but it increases to 1.7 cm during twisting movements (Bench data courtesy of Medtronic Inc.)

lead and its connector cable varies with flexion and extension of the spine and is also governed by the site of IPG implantation. Recent bench data indicates that a 9 cm displacement takes place between the upper buttock (site of IPG implant) and the thoracic spine (site of anchor) between flexion and extension of the dorsolumar spine (Fig. 5a, b). In contrast, when the IPG is located in the anterior abdominal wall, the strain on the lead is much less. In this situation, the excursion of the extension lead from the anchor to the IPG site on walking is 0.2 cm and on twisting 1.7 cm (Fig. 6a, b). This shows that the tensile load during regular activities changes according to the body position.

In order to reduce the tensile load on the lead during excursion of the extension cord with changes in body position, it is recommended that a strain relief loop is created between the anchor and IPG and where possible the IPG should be implanted in the anterior abdominal wall in preference to the gluteal location. To prevent the lead from slipping through the anchor it is suggested that a strong suture is used to secure the lead to the anchor and the use of a tissue adhesive inside of the anchor. Attention should be paid that the anchor is fixed to the deep fascia and not to the subcutaneous tissues to prevent it from being pulled away from its point of fixation.

The incidence of displacement is twice as high in patients with torsion scoliosis of the dorsolumbar spine and in the cervical regions. In such cases to prevent dislodgement, the use of paddle electrodes is preferable whenever possible.

Electrode fracture

In our series the incidence of electrode fracture was 6.37% as compared to the 9.1% in the literature [27]. The most common site of fracture in Pisces type of electrode was just distal to the site of the anchor where the lead exits the deep fascia. This is the site of the kink in the lead and is the point of stress where maximum bending fatigue occurs during flexion and extension of the spine, resulting in fracture. Recent bench data shows that the smaller the inside bend/kink radius, the greater the incidence of fracture. During the revision of the fractured electrodes, we found that the rate of fracture increases when the anchor is 1 cm or more beyond the point of exit of the lead from the deep fascia. This may be related to the reduced bend radius of the lead.

To reduce the incidence of fracture it is necessary to increase the degree of inside kink radius of the lead. This can be achieved by placing the three wing soft silicone anchor as close to the point of exit of the lead from the deep fascia or even pushing the nose of the anchor through the deep fascia (Fig. 7a, b).

The paramedian approach is preferred over a midline approach for implantation of percutaneous leads. The paramedian approach, by allowing for a much shallower angle of introduction, permits much easier steering and precise placement of the electrodes. The shallower angle of introduction also increases the inside kink radius when the lead is anchored to the deep fascia, which results in lower incidence of fracture.

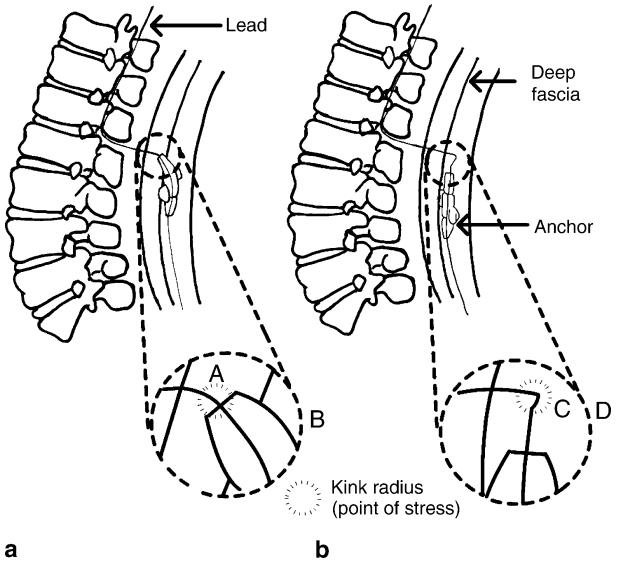

Fig. 7(a and b). Position of anchor decreases the kink radius. The position of the anchor decreases the degree of kink radius. The smaller the kink or bent radius, the higher the incidence of fractures. In Fig. 3a and b, the kink radius is increased by pushing the nose of the anchor through the deep fascia as compared to when the anchor is away from the point of exit of the lead in Fig. 3b (Bench data courtesy of Medtronic Inc.). *A* Increased kink radius, *B* anchor is pushed through the fascia to increase the kink radius, *C* decreased kink radius, *D* anchor not pushed through fascia

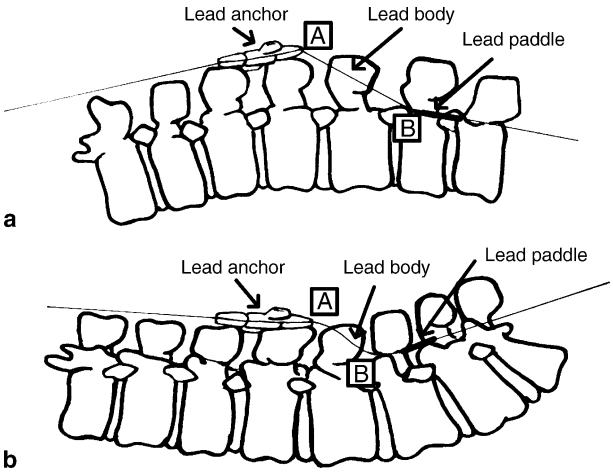

Fig. 8(a and b). Excursion of the lead of the paddle electrode on flexion and extension of the dorsal lumbar junction. The change in the lead path (distance between points A and B) being 2.1 cm (Bench data courtesy of Medtronic Inc.)

A fracture of the Paddle electrode is rare, but when it happens it usually occurs at the junction of the electrode to its lead. This is related to the fact that between flexion and extension there is 2.1 cm displacement between the dorsolumbar fascia where the lead is anchored (point A) and the epidural space where a paddle electrode is implanted (point B) (Fig. 8a, b). This places significant stress on the lead in between these two fixed points. These stress forces contribute to electrode fracture. To reduce the stress at these fixed points a strain relief loop is suggested.

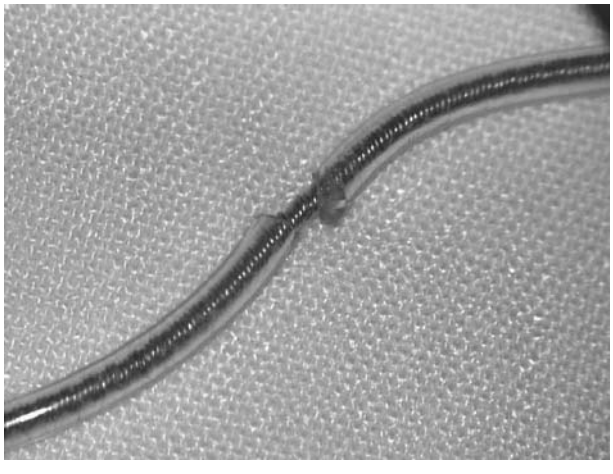

Fig. 9. Damage to the insulation and the internal coil by the plastic twist lock anchor

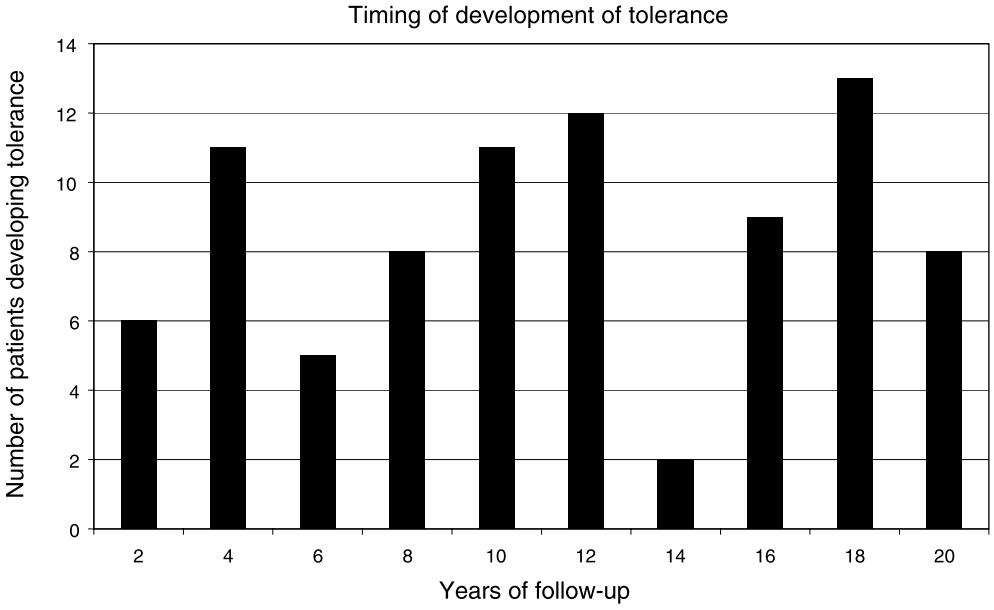

Fig. 10. Development of tolerance over time. Values indicate the number of patients developing new onset of tolerance during each 2 year period. The incidence of tolerance is scattered throughout the follow up period

The twist lock anchor causes a break in the insulation/coil of the lead (Fig. 9). This was observed in 9 cases in our series. This damage to the lead is caused by the pressure exerted by the twist lock mechanism of the anchor on the insulation and the stress caused by repeated flexion and extension of the spine at this point of fixation. We would therefore like to discourage the use of this anchoring device.

Infection

Infection is a serious biological complication of implant therapy and one of the most costly to rectify. The rate of infection in the literature is reported at 0–12% with a mean of 5% [12, 24, 26]. In our series, the rate of infection was 3.5% which falls at the lower end of the scale. To avoid this complication one must treat this procedure with the same aseptic techniques as implied in any major surgical procedure. The use of prophylactic antibiotics is recommended, which is not universal at the present time.

Other biological complication

Subcutaneous hematomas have an incidence of 0–9% in the literature [9, 27, 28] and occurred in 4.48% in our series. The smaller subcutaneous hematomas resolve spontaneously, however some require aspiration and rarely an open operation. Strict hemostasis at surgery and prompt aspiration are suggested to prevent wound dehiscence and subsequent infection.

Tolerance

Tolerance is defined as a progressive loss of pain control in the face of a fully functioning stimulating system. Tolerance has been the most significant cause of loss of pain control after long-term successful pain relief, occurring in 85 patients in our series. The incidence of this problem is scattered throughout our period of follow-up with no predictable pattern (Fig. 10). The exact mechanism of this phenomenon is not known. The use of amitriptyline, L-tryptophan or stimulation holidays in treating this problem has been met with minimal success. More research is warranted to overcome this obstacle and thus improve the long term success rate.

Acknowledgments

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Hardware failures in spinal cord stimulation (SCS) for chronic benign pain of spinal origin

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Summary

Spinal cord stimulation (SCS) has become an established clinical option for treatment of refractory chronic pain not related to cancer. Current hardware and implantation techniques for SCS are already highly developed and continuously improving, however equipment failures over the course of the long-term treatment are still encountered in a relatively high proportion of treated cases. Percutaneous SCS electrodes seem to be particularly prone to dislocation and insulation failures. This review summarizes the experience of the authors with management of hardware failures and their causes in patients treated with SCS for chronic pain of benign origin. The published literature is critically surveyed and discussed.

Keywords: Hardware failure; low back and leg pain; spinal cord stimulation.

Introduction

Spinal cord stimulation (SCS) has been evolving since its clinical introduction in the late 1960-ies to become a routinely used procedure in the clinical treatment of chronic pain conditions of benign spinal origin [4, 5, 8–10, 22, 24]. One of the complex pain syndromes most frequently treated by SCS is chronic back and leg pain (CBLP), often used synonymously with the so-called failed back surgery syndrome (FBSS). CBLP is a permanently disabling condition of multifactorial genesis occurring in 5–10% of patients with degenerative spinal disease [6, 11, 18]. Typically but not necessarily, CBLP patients have undergone multiple surgeries for disc herniation, lumbar stenosis, or degenerative spinal instability, and have developed adhesive arachnoiditis or epidural and intradural fibrosis resulting in severe radicular or pseudoradicular pain and low back pain [11]. In these patients, SCS is an effective and minimally invasive treatment modality and yields long-term results in 50–70% of the patients [2, 3, 13, 15–17, 20]. Although SCS hardware and surgical implantation techniques are currently well established and technically highly elaborate, there still are hardware failures caused by physical limitations of the used materials and by variations in the implantation techniques.

This review aims at identifying the most frequent types of hardware failures and their underlying causes in patients with chronic benign pain of spinal origin treated by long-term SCS. The experience of the authors and the pertinent literature are reviewed and compared.

Personal experience with SCS hardware failures

The authors have used SCS for treatment of chronic pain of benign origin since 1992 and have implanted more than 150 patients in total. There have been some dramatic technological improvements in the implantable and non-implantable equipment since the early 1990's; however an overview of the engineering achievements in SCS is beyond the scope of this article.

Out of the first 100 consecutive cases of the authors, a series of 42 patients with CBLP treated with long-term SCS has been investigated in detail [7]. Twenty-eight of these patients were female (66%) and 14 male (34%), with a median age for the whole group of 52 years (range 34–72). The median follow-up period for all patients was 46 months (range 6–74 months). Parameters included in the investigation were: time to failure after implantation of the device, frequency of failures, sites and types of failure, and overall duration of SCS. In all

but 4 patients of this series, percutaneously inserted quadripolar electrodes (PiscesQuad®, Medtronic Inc., Minneapolis, MN) were used. Single electrodes were implanted in 35 cases and dual electrodes in 3 cases. In 4 further patients, minimally invasive partial medial laminectomy was carried out under local anesthesia for placement of flat quadripolar surgical electrodes (Resume®, Medtronic Inc.). Radiofrequency receivers (model 3470, Medtronic Inc.) were implanted in 35 patients and X-trel® external pulse generators were used for stimulation. In the 3 patients with dual electrodes, an implantable dual channel radiofrequency receiver and external pulse generator (Mattrix®, Medtronic Inc.) were used. Patients used their SCS devices for a median time of 8.4 hours daily (range 1–24) over a total of 6,830 stimulation months.

A total of 12 (28.5%) surgical corrections of the hardware were carried out in this group of 42 patients. In 8 cases there was a single corrective procedure, in 2 additional cases two surgical corrections each were necessary: in one patient because of recurrent electrode failure and in the other patient for initial electrode failure and subsequent receiver failure. The most often encountered type of hardware failure was breakage of the electrode with partial or total disruption of insulation leading to short-circuiting and dysfunction ($n = 6$). In 2 additional cases, the electrode failed but the type of failure remained unknown. Only percutaneous PiscesQuad® electrodes were affected by such failures, while with Resume® electrodes no such failures were encountered. Second in frequency was receiver failure due to insulation leakage ($n = 2$) and extension cable breakage or disconnection ($n = 2$).

In order to compare hardware reliability and durability, we calculated the total time of stimulation time to failure (TF), which is the time period from implantation of the complete SCS system to the first surgical revision for a hardware failure. For all hardware failures, median TF was 24 months (range 5–37). For the PiscesQuad® electrodes alone, median TF was 15 months (range 4–29), and for the implanted receivers it was 23.5 months (range 10–37). In comparison, the median total time of SCS usage in our patient population was 57 months (range 6–74). We concluded therefore that hardware failures tend to occur relatively early during the course of long-term SCS treatment, and that this is particularly true for failures of the percutaneous electrodes. There was no correlation between hardware failures and subjective satisfaction of the patients. After surgical revision of the hardware the system was used in the same way and with the same effect as preoperatively [7].

In the last decade radiofrequency receivers and external pulse generators have been completely replaced by fully implantable single electrode pulse generators (IPG) such as Itrel-II® and Itrel-III® (Medtronic Inc.), or dual electrode IPGs such as Synergy® (Medtronic Inc.). With all these IPGs there is one additional problem – the need for periodic replacement of the IPG because of battery depletion. Stimulation parameters and energy requirements vary between patients and also in each single patient over the course of their long-term treatment, which effectively precludes comparisons of mean battery life of the different IPG types between our patients with fully implantable SCS systems and other cohorts in the literature. On the other hand, electrode types and materials have changed little over the course of the last decade and we were unable to ascertain any significant differences in the type and frequency of electrode failures in patients with radiofrequency receivers versus those with IPGs in our whole series.

Hardware failures of SCS in the literature

Detailed data on SCS hardware failures are relatively rare in the literature. A few studies provide information on hardware failures in the context of data on SCS efficacy and safety. Broggi *et al.* treated non-malignant chronic pain in 410 patients in a multicenter study and reported 3% technical complications during the 2 years follow-up [3]. Barolat [1] reported only 4 hardware failures in a large series of 509 implanted electrodes, however all of these were surgical electrodes which are sturdier and more resistant than percutaneous electrodes. Bel and Bauer [2] analyzed 18 SCS patients with a mean follow-up time of 24 months and reported electrode breakage in 7 patients (39%). In 5 of these cases, the failure occurred spontaneously and in 2 cases there was an underlying trauma. North *et al.* published a large series of 298 SCS systems in 249 patients with a mean follow-up time of 7 years. There were 22 electrode failures (fatigue fracture, insulation failure) and 16 additional receiver failures in the whole series [16].

Turner *et al*. evaluated 39 published studies in a metaanalysis and calculated total hardware complications from the bulk of available data [17]. Across a variable number of evaluable studies, 30% of patients had one or more hardware-related complications (range 0–75%), 24% had electrode insulation failures (range 0–75%), 7% electrode wire failures (range 0–24%), and 2% (range 0–9%) IPG failures [24]. Turner *et al*. updated their initial review in 2004 to include efficacy and complications

of SCS for CBLP and for complex regional pain syndrome (CRPS). These authors evaluated a total of 22 studies with an average follow-up time of 4 years or less [25]. The median percentage of hardware failures across all studies was 6.5% (range 0–40). In addition, IPG revisions for reasons other than depleted battery (including electrode displacement) were carried out in a median of 21.5% of cases (range 0–81%). The authors concluded that because of widely variable follow-up times and reporting patterns for hardware failures it was difficult if not impossible to perform a detailed comparison of all types of hardware failures [25].

Quigley *et al.* reported their 11-years retrospective experience with SCS for long-term pain relief in 102 patients. The authors carried out a total of 64 (62.7%) hardware revision operations on 35 patients. Hardware failures included replacement or repositioning of electrodes ($n = 29$), IPG replacement ($n = 23$), extension cable failure ($n = 3$), and total removal of SCS system ($n = 5$). Despite this relatively high frequency of hardware failures, there was substantial clinician-reported long-term pain relief in 69 (68%) of cases [19].

Taylor *et al.* recently conducted a systematic review and analysis of prognostic factors in SCS for CBLP. Although the authors reviewed a total of 74 studies, SCS complications data from only 18 studies could be utilized due to the common failure of mixed case series to report complications disaggregated by diagnosis, and due to the fact that numbers of complications were reported rather than the number of patients who experienced them. Overall, 43% (48/112) of patients with CBLP experienced some SCS hardware failures. The majority of these were due to electrode failures (27%, 195/722). IPG failures were seen in another 6% and extension cable failures in 10% of the patients [23].

North *et al.* carried out one of the very few prospective and controlled clinical trials for postoperative CBLP, which compared single and dual percutaneous SCS electrodes. The authors evaluated 20 patients who passed SCS screening with single electrodes and received permanent dual electrodes at the same vertebral levels. Despite the high overall quality of the study, hardware failures were reported only in passing and without sufficient detail. Electrode migration in one patient and IPG failure in another patient required surgical revisions, resulting in a total hardware failure rate of 10%. Clinical failure led to the removal of implants in 4 patients (20%) after an average of only 0.9 years (range 0.5–1.4). A successful long-term outcome was achieved in 53% of patients [14]. North *et al.* conducted another prospective, randomized and controlled trial in patients with persistent radicular pain to test if SCS is more likely than reoperation to result in a successful outcome. Average follow-up after SCS implantation was 3 years. A total of 45 patients (90% of original sample) were available for follow-up. Three SCS patients (9% of permanent implants) underwent surgical revisions because of hardware failures (electrode dislocation). No further details on hardware failures were given in this study [12].

Discussion

Electrode dysfunction was the most common hardware failure in our own series of long-term SCS patients. This type of hardware failure cannot be detected by X-rays in all cases, but should always be suspected when a sudden disappearance of paresthesia in the painful dermatomes or appearance of differently located (ventrolateral) sensations are experienced. Disruption of insulation causes short-circuiting and electrode dysfunction and may be caused or facilitated by superficial injuries of the electrode insulation by the edge of the percutaneous implantation needle during surgery. Minor cuts are probably combined later with increased axial tension stress and hypermobility of the percutaneous electrode in the spinal canal to finally result in disruption of the plastic insulation or/and of the electrode wire. Sometimes the failure occurs immediately after a traumatic event and then it is usually caused by mechanical overload of the material.

True radiofrequency receiver failures are probably a very rare event because of the simplicity of the device (model 3470, Medtronic Inc.). With IPGs, hardware failures seem to be uncommon as well, however these fully implantable devices need periodic replacement because of battery depletion. With both types of implanted devices, the weakest point seems to be the connection between the extension cable plug and the device. We have seen 2 cases of receiver failure by short circuiting due to leaks in the insulation at the plug connection. Special attention has to be paid to inserting the connecting plug of the extension cable into the receiver as tightly as possible and waterproofing it with some silicon-based glue.

Comparison of the published literature with our own experience with hardware failures is very difficult because of the lack of standardized evaluation. The only meaningful conclusion resulting from such variability of reported data is that management of hardware failures remains an integral part of the routine follow-up

management of patients with long-term SCS for CBLP. Electrode failures are the most common type of hardware failure in our experience and in the series of others, and are usually dealt with by surgical revision and electrode replacement. It is not possible to identify specific causes for hardware failures, however a common trend in all studies is that percutaneous electrodes (e.g. such as PiscesQuad®) are more prone to failure than surgical electrodes (e.g. Resume®). The weakest part of all SCS hardware seems to be the percutaneous electrode. We believe that some electrode failures may be avoided by better handling during implantation and by appropriate surgical technique. It should be noted that hardware failures, unlike loss of efficacy of SCS, are most often of sudden occurrence.

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Minimally invasive placement of epidural plate electrodes under local anaesthesia in spinal cord stimulation

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Summary

In the treatment of pain syndromes of different aetiologies a change has occurred from destructive interventions to stimulation procedures. Spinal cord stimulation is the best known example of this treatment strategy. It is used often in patients with persistent neuropathic pain syndromes in an extremity, for instance following low back surgery. This treatment is most frequently performed by a percutaneous placement of a single electrode, with the aid of a specially designed Tuohy needle to reach the epidural space. In cases where, for different reasons, a larger, plate electrode is needed, this has to be placed surgically by a small laminectomy. The general anaesthesia mostly needed for this procedure prevents trial stimulation necessary to check the correct electrode position. Besides this, the laminectomy procedure can subsequently result in new pain complaints due to the invasiveness of the procedure. To solve both problems we have modified the implantation technique. By using a tubular retractor system (METRx® system, Medtronic Sofamor Danek®, Memphis, TN), originally developed for minimally invasive degenerative disc surgery, it is possible to reach the epidural spinal space and introduce the plate electrode with a small approach under local anaesthesia both allowing trial stimulation and avoiding severe postoperative backache related to the approach in these patients.

Keywords: Epidural plate electrode; METRx® tubular retractor system; minimally invasive; spinal cord stimulation.

Introduction

Pain relief by spinal cord stimulation (SCS) is a well-accepted treatment for selected patients with persistent neuropathic pain syndromes, e.g. after spinal surgery, since the early 1970's [5, 8].

Routinely, for back pain radiating in the leg, we percutaneously implant a quadripolar lead with four platinum iridium electrodes on the distal end (Pisces Quad™ Compact Medtronic, Kerkrade, The Netherlands) by use of a Tuohy needle, connected to a single channel stimulator (Itrel® III). However, suboptimal electrode placement or recurrent dislocation can necessitate electrode revision. Also, stimulation using high amplitudes rapidly decreases the life span of the stimulator. Therefore, despite major advances in electrode design such as multichannel stimulation and increased battery capacity, failures still frequently occur [9, 11].

Alternative electrode configurations with larger stimulating areas (e.g. multi-channel, eight electrodes; Specify® lead, Medtronic) can result in an improved coverage of the painful area and a better effect on pain, combined with a lower battery current due to a larger contact with the dura [5, 12]. From a technical point of view a better electrode fixation also seems possible.

These larger plate electrodes, however, could only be inserted epidurally by means of a (small) open surgical procedure involving a partial laminectomy. It is difficult to perform this procedure under local anesthesia (and sedation). In a recent publication, Lind *et al.* [4] therefore described a technique using spinal anaesthesia to implant these electrodes diminishing the discomfort for the patient and maintaining the possibility to perform intra-operative test stimulation. However, by using this technique, postoperative recovery can still be hampered by the relatively large incision and the wide stripping of the paravertebral muscles with subsequent pain complaints.

Therefore, we describe a (modified) technique in which the plate electrode (Specify®, Medtronic) can be inserted epidurally under local anesthesia (and sedation) by a minimally invasive procedure with no need to strip the paravertebral musculature, using the METRx™ tubular retractor system (Medtronic Sofamor Danek, Minneapolis, MN, USA). The METRx™ tubular retractor system is developed to approach the spinal column by spreading the paraspinal muscle fibres in a sub

sequential way by enlarging tubes, thereby avoiding the need to strip these muscles from the bone. The final working channel is provided by a tube with a maximum diameter of 18 or 22 mm. The technique has been adapted for other indications by others [3, 10]; we decided to adapt the technique for the minimally invasive placement of SCS plate electrodes, making it possible to perform the procedure under local anaesthesia with little postoperative pain complaints.

Patients and methods

From December 2002, we use this technique in patients who need to be treated with a SCS plate electrode. The majority of them were treated with spinal cord stimulation because of failed back surgery syndrome (FBSS). Most of them had a partial effect of a conventional percutaneous electrode and inadequate stimulation area compared to their painful region. In all these patients, unilateral leg pain predominated the presence of minimal back pain. Despite previous percutaneous revisions, electrode displacement during follow-up occurred leading to a decrease of stimulation coverage. Some other patients needed frequent changes of the Itrel (every nine to ten months) due to a high stimulation intensity. The area covered by stimulation was adequate. One patient was operated for a thoracic neuropathic pain syndrome following removal of an intramedullary dermoid tumour at the 3rd and 4th thoracic vertebra. Initial placement using a larger Specify® electrode via this method was undertaken since we expected epidural fibrosis.

Surgical technique

Following standard antibiotic prophylaxis (cefazolin 1000 mg. i.v. one hour preoperatively and six hours postoperatively) and oral pre-medication (midazolam 7.5 mg and acetaminophen 1000 mg), patients are placed prone on the operating table, as usual for dorsal spinal procedures taking care that biplane X-rays of the lumbar-thoracic spine are possible. Standard anaesthetic monitoring for general anesthesia is used. After radiographic orientation, the desired level of entrance of the new electrode is marked. This is determined by the interlaminar area one level below the desired epidural position, usually covered by the present electrode. Desinfection, aseptic draping of the surgical area and extensive local anesthesia (xylocaine 1% with adrenaline 1:200.000) take place accompanied by

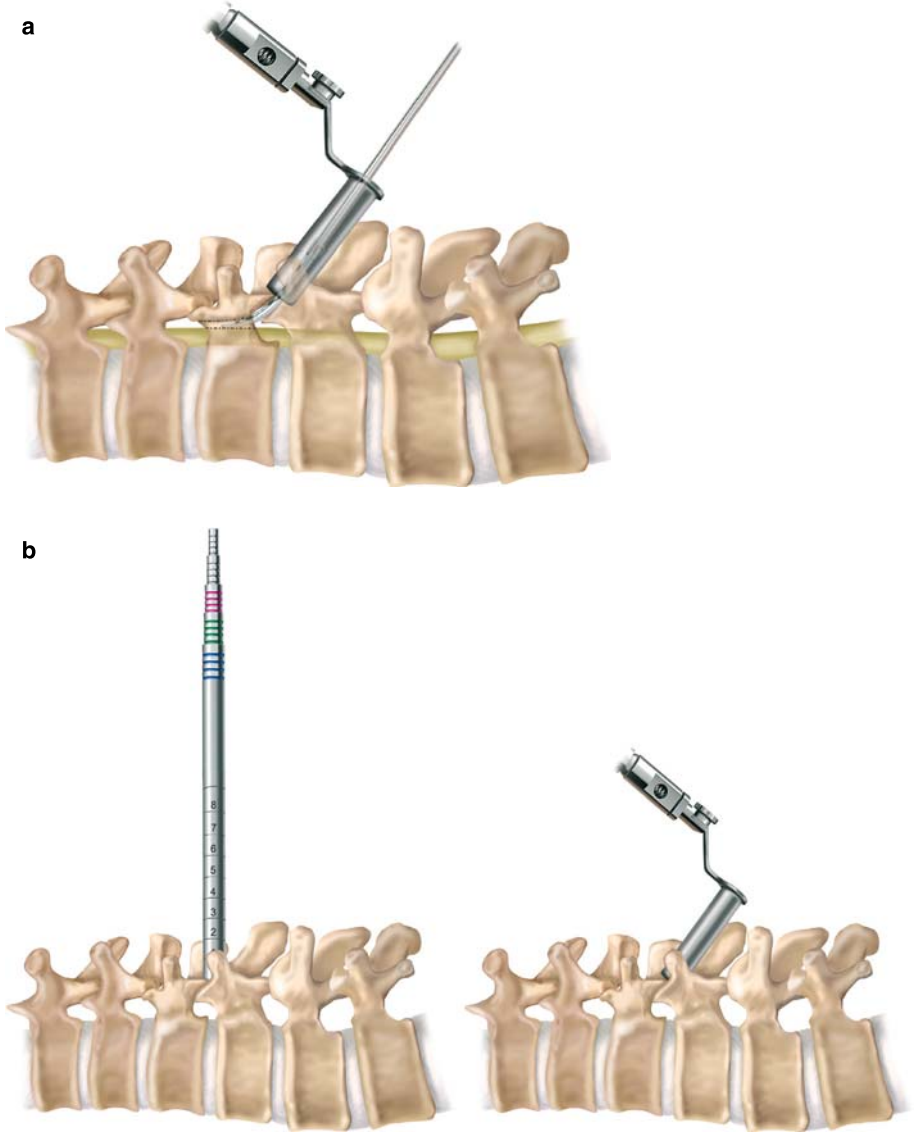

Fig. 1. Schematic drawing of the electrode and tube position in relation to the spine (a). Compare the tube position in disc surgery (b – left) to the tube position for SCS plate electrode insertion (b – right). This change in direction is necessary for an uneventful introduction (without dura compression) of the surgical stimulation lead in the dorsal epidural space

intravenous sedation with propofol and low dose fentanyl by an anesthesiologist. These are dosed to an acceptable level of sedation and pain relief. In our experience this provide good operative conditions.

Before starting the procedure the initial electrode is located and removed through a small incision at the level of the interspinous entrance where the electrode is fixed to the fascia as well as at the level of the connection with the extension lead. Thereafter, a small, 10–12 mm long paravertebral incision is performed about 1.5 cm lateral to the spinous process at the side of the persistent pain, slightly below the level of the interlaminar space that is to be opened. This approach is used to anticipate possible adhesions making midline crossing more difficult. During the procedure verification of this level is determined by frequent fluoroscopy. The paravertebral muscle fascia is sharply opened about 1 cm in length because we have to follow a medio-cephalad tube direction to the spinal column. This must be done to be able to introduce the stimulation electrode in the epidural space without pressing the dura unnecessarily later in the procedure. (Fig. 1a) This is in contrast with the perpendicular route to the spine when using the METRx™ system in disc surgery. (Fig. 1b) A disadvantage of our approach is a partial dilatation of the fascia with the subsequent tubes after introduction of the guidance pin of the Mettrx™ system due to the angle of insertion. This can make it impossible to reach the fascia with all sides of the tubes simultaneously. Subsequent enlarging and opening of the fascia can therefore be difficult. After opening the fascia, the inferior border of the superior lamina at the desired interlaminar space is approached and confirmed by fluoroscopy. Thereafter, dilating tubes are placed sequentially until a 18–22 mm diameter retractor tube (depending on the surgeons experience) can be inserted. This exposes the caudal part of the superior lamina, the flava ligament and the superior margin of the inferior lamina. Frequent fluoroscopy is used to prevent an undesired cephalad disorientation due to the steep angle of approach. Thereafter the retractor is stabilised and fixed to the operating table by means of the flexible arm of the system (Fig. 2).

To improve exposure and illumination a partial caudal hemilaminectomy and removal of the ligamentum flavum using small Kerrisons are performed under microscopic guidance. It is important that the hemilaminectomy includes the lateral aspect up to the medial facet joint and crosses slightly over the midline to be able to move the electrode in the desired direction. It is not always necessary to enlarge the interlaminar space in a more caudal direction, but when the interlaminar space is very small it can be considered to remove a small part of the inferior lamina by this approach as well.

Since the standard plastic instrument supplied with the Specify® lead to dissect adhesions in the epidural space, has too sharp curvature to be inserted through the tubes, we modified this manually during the procedure. Removal of the very distal (1.5 cm) part of this instrument with a scissor was undertaken carefully. Then adequate insertion of this modified instrument through the working channel is possible in order to perform a small epidural adhesiolysis in the same way as it is done in an open procedure. This makes it possible to insert the electrode into the epidural space without technical problems. It is possible that the adhesions are too tight. But the difficulty to remove the adhesions is the same as in an open procedure, only with less working space. We encountered failure in removing adhesions with this approach in only two patients. One was due to an operation at the same level because of an intramedullary dermoid cyst; the adhesions to the lamina were to strong to be removed through the tube making it impossible to enter the epidural space. In the other case the epidural adhesions were too resistant to be released and needed a larger approach. In all other cases, insertion of the electrode was possible. Further cephalad manipulation in the epidural space is performed with a specially designed, slightly curved tool in all patients without problems (Fig. 3). This instrument partly encroaches the flexible plate electrode making it more steerable, since the electrode cannot bend sideward when fitted in this tool. It is easier to reach the right position in this way, but sometimes it can be difficult to dissect all adhesions as in an open procedure. We therefore always choose to open the epidural space at the side of pain complaints. When crossing the midline in these cases is

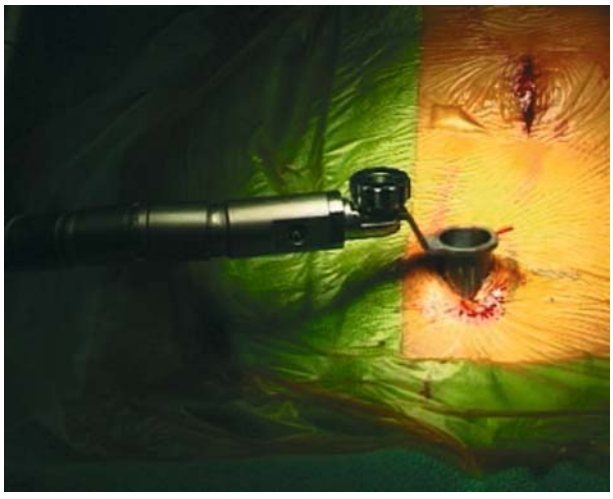

Fig. 2. The working tube is fixed in position with a flexible retractor that is connected to the operation table. Note that the incision for removal of the percutaneous lead (in the top of the image) is larger than the incision needed for the tube placement

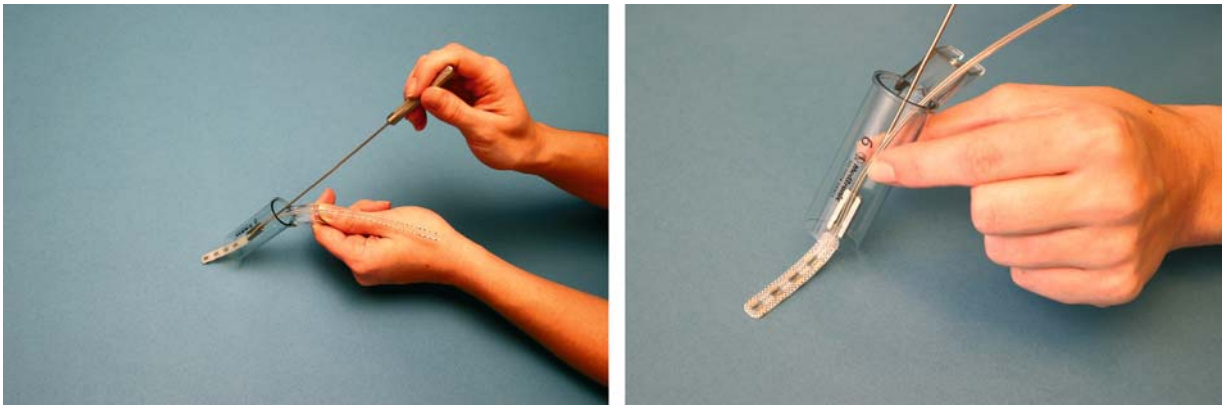

Fig. 3. Photograph of a Specify plate electrode (*overview on the left*, *detail on the right*) in the specially designed introducer. Note that the introducer encroaches the (flexible) electrode partially, making sideway movements less possible and the electrode more steerable. The shaft of the introducer is bendable allowing adjustment of the shape (bayonet), making the tip visible according to the situation

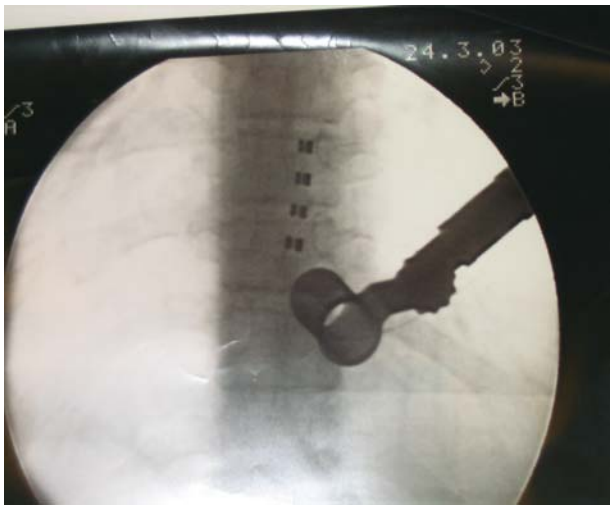

Fig. 4. Fluoroscopic image controlling the lead location after epidural placement and before trial stimulation. The lead is positioned slightly paramedially on the right side due to persistent adhesions in the midline that could not be released. Note the (*slightly caudal*) position and (*paramedian*, *cephalad*) direction of the working tube in relationship to the position of the lead

not completely feasible for the lead to be placed at the right side. In some cases this can also be performed with a forceps. After confirmation of the position of the lead by fluoroscopy (Fig. 4) the sedation is diminished. Test stimulation is performed in the usual manner with the help of an extension cable and screener. Following confirmation of the correct position of the lead, the tubular retractor is removed keeping the plate electrode in the same position by fixing the cables with a forceps. The lead cables are fixed to the fascia in the usual way which is challenging because of the small incision.

The fascia incision is closed with the same sutures. Fixation of the plate electrodes to the lamina is never performed in our institution. The leads are connected to the extension cables connected to the pulse stimulator already present (or an extension lead and stimulator device are placed in the usual way) and skin closure is performed intracutaneously.

Results

Except for two patients (one had been operated at the level where the electrode entrance was planned and one had extensive epidural adhesions), insertion was uneventful, in spite of the fact that all patients had already an electrode implanted before at the same level and the interlaminary distance was sometimes very small. Optimal electrode position and adequate stimulation were accomplished in all patients in whom we were able to insert the electrode to the desired location. The electrodes were both connected to a Synergy® system which makes dual stimulation possible. We did not encounter problems with the trial stimulation because the sedation level could easily be diminished and all patients could respond adequately with normal trial stimulation thresholds.

The patients who were operated on because of inadequate, partial stimulation of the affected dermatomes noted better stimulation coverage with the plate electrode. In all patients with frequent dislocations of the percutaneous electrode, very good coverage of the affected pain area was obtained and this persisted in the follow-up of 30 months. The patients with high voltage used (and short life-span of battery) had persistent good pain relief with a 50–60% reduction in amplitude; a longer use of the implanted system is thus expected.

In the patient with the former operation at the same spinal level, the procedure could not be performed, because the adhesions were too tight to be released from the lamina through the tube, so we were not able to reach the epidural space safely and decided to convert the procedure to an open laminectomy two weeks later (with a satisfying result). Only in one patient we were not able to position the electrode at an optimal location because we were not able to remove the epidural adhesions from the former electrode adequately. This problem is also encountered in open procedures. This patient needed a wider laminectomy through an open procedure under general anesthesia. (We were able to confirm the right spinal level by trial stimulation in the minimally invasive procedure.) In the patients treated successfully with the minimally invasive tubular approach, operation-related pain complaints could be treated with minor analgesics (acetaminophen, 1000 mg 4 times a day), after a first postoperative opioid dose. Postoperative recovery was uneventful and mobilisation on the first postoperative day was possible in all patients.

We had one post-operative complication. A patient (who formerly had inadequate coverage of the pain area by a single electrode) experienced an increase in urinary problems, necessitating frequent bladder catheterisation. She already had urinary retentions and incontinence before this procedure. Post-operative urological evaluation showed a previously dilated and partial denervated bladder. No signs of neurological bladder dysfunction i.e. due to spinal cord or caudal compression were present. Since her discharge, these complaints have not disappeared and the patient still performs intermittent self-catheterisation of her urinary bladder. Pain relief was satisfactorily and she had only minor approach-related complaints. These good results persisted after more than one year of follow-up.

Discussion

SCS has proven to be effective in patients with a variety of therapy-resistant neuropathic pain syndromes e.g. following ‘‘failed back’’ surgery, especially when pain

radiates into a leg and previous interventions have proven ineffective. In the majority of patients the electrodes can be placed percutaneously in the epidural space using a specially designed Tuohy needle and X-ray control [6]. However, in a number of cases, this technique can fail due to inability to reach all the selected dermatomes with the electrode (due to epidural adhesions) and failure to cover the painful area adequately via a single lead. Furthermore, the need for a high-energy output by the stimulator makes frequent change of the stimulator necessary and can also be a cause of ''failure''.

In these cases, therefore, surgical placement of a larger ''dual'' lead can be considered [5]. In addition, the shorter distance from epidural space to spinal cord due to a larger surface area may explain reductions in the required electric output of the stimulator [7, 12]. Until now a classical, larger intervention using a (hemi-)laminectomy under general anesthesia was necessary. This approach causes an increased intra- and post-operative discomfort for these patients, due to the needed wide stripping of the paravertebral muscles from the spinal bone. Therefore, this surgical intervention is often withheld in these patients because of the unpredictable nature of the procedure during general anesthesia and the impossibility to stimulate intra-operatively. This problem urged Lind *et al.* [4] to develop a technique using spinal anesthesia. They reported that trial stimulation is still possible in these circumstances and that the procedure minimizes the discomfort of the patient, although the post-operative pain complaints using this technique remain the same. Instead of adapting the anesthetic technique we decided to modify the surgical approach, in order to perform the procedure using local anesthesia. By a minimal invasive technique, spreading the paravertebral muscle fibers using sequentially enlarging tubes instead of stripping them from the spine, we demonstrated that it is possible to insert these larger epidural electrodes under local anesthesia, making trial stimulation with these electrodes possible, and avoiding the postoperative complaints due to muscle splitting. In our view, this adds an extra argument in favour of this plate electrode technique since the stimulation possibilities of these leads are increased. We used the METRx^{TM} tubular retractor system, which is used for percutaneous, endoscopic removal of lumbar disc herniations [1], but later used for other minimally invasive spinal procedures as well [3, 10]. Clearly some changes of the technique are necessary for this specific purpose. The approach of the spine is different compared with the approach for disc surgery. Some instruments were modified by ourselves and an introducer was developed (Fig. 3). Further modifications of the instruments will make insertion of the leads probably even easier.

The excellent technical results so far, in difficult cases after revision surgery, and the satisfaction of the patients both with the procedure itself and the little postoperative pain complaints lead us to conclude that this technique can be considered a very useful alternative to the classical operative procedure for inserting dual lead electrodes. It can be offered to patients with a good, but only partial effect after single lead stimulation or to patients with a short stimulator life-span due to use of high amplitudes. It remains to be seen whether this technique will replace the classical percutaneous technique in the future. A prerequisite, however, is a well-motivated patient willing and able to detect electrical stimulation perioperatively under local anesthesia.

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Implantation of surgical electrodes for spinal cord stimulation: classical midline laminotomy technique versus minimal invasive unilateral technique combined with spinal anaesthesia

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Summary

The implantation of surgical electrodes is still considered painful and invasive. Is there a possibility to diminish these disadvantages by applying a less invasive implantation procedure at the thoracic level and eventually combine this approach with a less stressful paresthesia coverage testing in the intraoperatively awake patient? In this paper, the postoperative outcome of two surgical techniques to insert surgical plate electrodes at the thoracic level is compared. In a prospective single blind study, the Classical Midline Laminotomy technique (CML) is opposed to a Minimal Invasive unilateral Technique (MIT). There were ten patients in each group, allocated at random. Postoperative pain was measured by an unbiased third party on the first and third day after electrode implantation using the Visual Analogue Scale (VAS) score. Length of hospital stay was compared in both groups. Patients were asked if they would, if necessary, undergo the same procedure again. In all comparisons, the MIT group scored significantly better. It can be concluded that a minimal invasive unilateral technique has some advantages over midline laminotomy. Refinements of the implantation procedure are discussed, i.e minimal invasive unilateral technique in combination with spinal (intrathecal) anaesthesia, surgical hints and the technique's use in revision surgery for migrated electrodes.

Keywords: Dorsal column activation; spinal cord stimulation; surgical electrodes; surgical technique; spinal anaesthesia.

Introduction

Classical indications for implantation of surgical electrodes include: a) replacement of percutaneous test electrodes after positive trial, b) frequent migrations of percutaneous electrodes, and c) surgery in the predicted target area [4]. In some centers, surgical electrodes are used as first choice, depending on the level of collaboration between the neurosurgical and anaesthesiological departments and the reimbursement policies of governments or health insurance organizations. Surgical electrodes for spinal cord stimulation have technical advantages compared to percutaneous electrodes. North showed a broader stimulation pattern and lower stimulation requirements of surgical electrodes [3]. Villavicencio saw that surgical electrodes appeared to be associated with better long-term effectiveness [7]. Percutaneous electrodes may be associated with a higher rate of migration; electrode migration could be the most common reason for failure to maintain long-term pain control with spinal cord stimulation [5]. The disadvantage, however, of the surgical electrode is the required surgery and its postoperative consequences. Meyerson, in his comment on the paper of North, wrote that neurosurgeons should strive to minimize the invasiveness of the surgical procedure and the discomfort to the patient [3]. Therefore, a minimal invasive technique should aim at reducing the disadvantages (postoperative pain, general anaesthesia or the stress of a procedure under local anesthesia) and preferably be combined with an intraoperative awake paresthesia coverage testing; certainly, if the surgical electrode is the first electrode a patient receives, the ideal position of the implant has to be determined during the surgical procedure.

Comparative study concerning postoperative outcome

Materials and methods

Twenty patients requiring an electrode at the thoracic level for spinal cord stimulation were selected at random to undergo MIT or CML technique. The patients themselves did not know which technique was to be applied. In all patients, a Specify electrode (Medtronic Inc., Minneapolis, MN) was used. All twenty patients suffered from neuropathic pain in one or both legs with or without low back pain, and all had

undergone previous lumbar surgery. There were eleven female and nine male patients. All surgical procedures were performed by the same surgeon, being the author.

The CML technique commences with a midline approach and bilateral subperiosteal dissection of the paravertebral muscles, using electrocautery. Then, after cutting the interspinous ligament, the inferior portion of the superior spinous process is resected and a limited midline laminotomy is performed with the aid of a Kerrison rongeur. After partial flavectomy, the dura is exposed. Usually, a local anaesthetic is administered in combination with propofol sedation. In some cases, general anaesthesia was induced. The position of the electrode is visualised by fluoroscopy. Using tunnelling devices, the disposable leads are externalized at the patient's flank.

The MIT technique has been performed in our department since 2002. A small incision on the midline of about 2 cm at the chosen level is done after injection of a long-acting local anaesthetic into the skin and the paravertebral muscles at one side of the spinous process. Meanwhile the patient has received propofol sedation. After unilateral subperiosteal dissection with electrocautery, a retractor for micro-lumbar discectomy (Caspar retractor, Aesculap) is installed. I prefer the Caspar retractor because it is widely used in all kinds of spinal surgery; it provides good visibility and offers good manipulation of the microsurgical spine instrumentation. I did not have the same feeling with a tubular retractor system. With a high speed drill with a 6 mm diamond burr head, the median third of the lamina and the transition of the lamina to the spineous process of the superior vertebra is undermined (Fig. 1). After partial flavectomy with a 1 or 2 mm Kerrison rongeur, the dura is exposed up to the midline. When using a Caspar retractor, haemostasis of epidural veins or of small blood vessels in the epidural fat tissue is no problem: visibility is very good (using head light and magnifying goggles) and bipolar cautery or the use of bone wax is easy. Then, since some space under the spineous process has been created, a surgical electrode can easily be inserted at the midline [6] (Fig. 2). There is no problem with pushing up the electrode in the spinal canal by two or three levels while keeping it straight on the midline (Fig. 3). The surgical electrodes are rigid enough to be raised without encountering too much resistance. Finally, the disposable leads are externalized at the patient's flank as it is done with CML technique.

This unilateral technique might resemble the microsurgical approach for lumbar disc herniectomy, but there is one main difference: in case of a herniectomy you will want to end up in the lateral part of the spinal canal, for an electrode you will want your approach to end up as medially as possible.

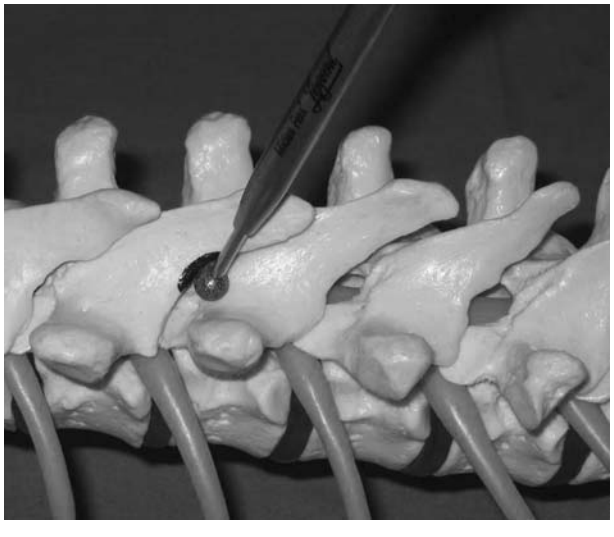

Fig. 1. High-speed is used to undermine the median third of the lamina and the area of transition to the spineous process

Fig. 2. The electrode is inserted into the midline epidural space

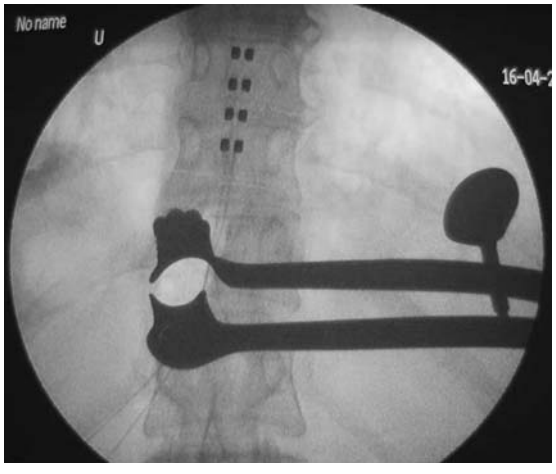

Fig. 3. Under fluoroscopic control, the electrode is advanced by two – three spinal levels into the epidural space

During the first postoperative days, both groups received the same analgesics according to a fixed scheme but with the option to ask for more. In this period, patients were interrogated by an unbiased third party.

Results

To assess the postoperative pain, the VAS score was compared between the two groups on the first and third postoperative day.

The CML group had a mean VAS score of 4 (3–6) against 2.3 (1–3) of the MIT group on the first postop. day; this is a statistically significant difference ($p = 0.00046$). On the third postoperative day, the score was 3 (2–6) for the CML group as against 1.6 (1–3) for the MIT group; which is also a significant difference ($p = 0.00124$).

Mean hospital stay for the CML group was 4.1 (4–5) days versus 3.2 (3–4) days for the MIT group being a statistically significant difference ($p = 0.00021$).

In the CML group, 70% of the patients would undergo the operation again, if necessary, versus 90% in the MIT group.

Conclusion

In this prospective single blind study with an independent observer, the minimal invasive unilateral technique for implantation of surgical electrodes at the thoracic level was shown to have several advantages as compared to the classical midline laminotomy including less local discomfort on the first days and a shorter hospital stay. This can possibly be explained by the smaller muscular trauma in a unilateral approach as compared with a midline approach for laminotomy. Another explanation could be that in a unilateral approach, the interspinous ligament and its innervation are not touched while in midline laminotomy, this ligament is intersected at the operated level.

Use of spinal anaesthesia and technical recommendations

At present, the MIT technique at the thoracic level in our department is performed in combination with spinal (intrathecal) anaesthesia, as described by the neurosurgeons from Karolinska hospital in Stockholm [2]. This means the patient is intraoperatively fully conscious, painfree and very cooperative in contrast to the procedure with propofol sedation and local anaesthesia. *Using this protocol, the MIT technique combines the advantages of a fully awake implantation of surgical electrode with less postoperative discomfort.* We call it the ''Duffel technique'' (Fig. 4).

There are many important issues to be borne in mind while performing an awake procedure in order to correctly position your surgical electrode. If a surgical lead is used with two columns (Specify, Medtronic Inc., Minneapolis, MN), it is very important to place your electrode as straight as possible on the midline of the spinal canal. When performing the awake test of paresthaesia coverage of the target area, it is possible that the painful area might well be covered although the electrode is positioned in a rather oblique position on the midline or straight up but laterally to the spinal canal. One should not be tempted to stop the procedure at this point because there is a risk of electrode migration within the next few weeks. Surgical electrodes can migrate too. It is important to point out that a good cover of paresthesia alone during an awake procedure does not necessarily mean long-term good results. The surgeon should always try to position the electrode as close as possible to the midline. An additional argument for this is that later on, reprogramming of the electrode might be required. Neuropathic pain treatment is indeed a dynamic process [1]. In such a case, there are as many programming possibilities as necessary if the electrode is positioned as correctly as possible on the midline. Naturally, this applies also to surgical plate electrodes with two columns, one on either side, just lateral but parallel to the midline.

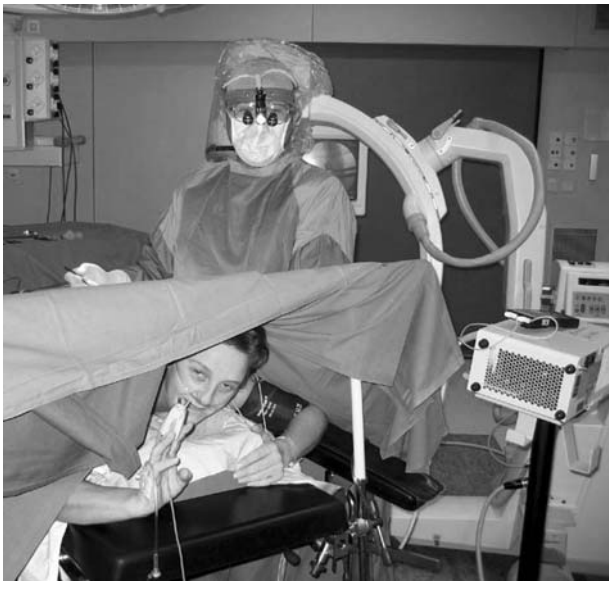

Fig. 4. Position and arrangement of the patient, the surgeon and the equipment in the fluoroscopic operation room (Duffel technique)

When performing an awake procedure it might be necessary that in order to get paresthesias in the lumbosacral region you have to move your electrode up to level D8D9, depending on the information obtained from the patient at the very moment of paresthesia testing. As already mentioned above, technicalwise there is no problem to raise the surgical electrode straight up by two or three levels away from the level of insertion. Be sure, however, that the patient does not confuse paresthesias in his loin or flank with paresthesias in his lower back. At a higher thoracic level, there is an increased risk of stimulating the intercostal regions.

For an experienced surgeon average time needed for the MIT approach, to position the electrode, to do the awake testing, and to close the wounds amounts to about 70 minutes. Spinal anesthesia in combination with local anaesthesia so far has covered the duration of the procedure without problems in all of our 15 cases. Mostly 20 mg of bupivacaine was given and injected intrathecally at level L2L3. In one patient with a moderate contra-indication for intrathecal anaesthesia, we even used successfully an epidural anesthesia at the thoracic level to implant our surgical electrode.

We also use the MIT technique for revision surgery, mainly in cases of lateral displacement of the electrode. At the level of plate electrode (and not at the level of

insertion into the spinal canal), a small unilateral interlaminar approach is performed, the fibrous coat around the electrode is removed, and the position is adjusted. If necessary, the electrode then can easily be fixed at the dura mater with a monofilament (5/0) suture.

The minimal invasive unilateral technique at the thoracic level combined with spinal anaesthesia has not shown any technical limitations so far.

Data can thus easily be gathered intraoperatively for further studies to compare different stimulation techniques at different levels in the same patient.

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Peripheral nerve stimulation for the treatment of neuropathic craniofacial pain

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Summary

Treatment of neuropathic pain in the region of head and face presents a challenging problem for pain specialists. In particular, those patients who do not respond to conventional treatment modalities usually continue to suffer from pain due to lack of reliable medical and surgical approaches. Peripheral nerve stimulation (PNS) has been used for treatment of neuropathic pain for many decades, but only recently it has been systematically applied to the craniofacial region. Here we summarize published experience with PNS in treatment of craniofacial pain and discuss some technical details of the craniofacial PNS procedure.

Keywords: Facial pain; neurostimulation; occipital nerve; occipital neuralgia; trigeminal nerve.

Introduction

When one describes use of peripheral nerve stimulation (PNS) in the treatment of craniofacial pain, the idea of a new and unusual application of the neuromodulation approach immediately comes to mind. The interest to this modality has been increasing over the last few years, but in fact, this use of electrical stimulation is anything but new. When about 40 years ago Wall and Sweet tried to find a new approach for suppression of neuropathic pain, they inserted an electrode into their own infraorbital foramina and obtained decrease in pain perception during the entire episode of electrical stimulation [41, 46]. Moreover, in the first article dedicated to the idea of peripheral nerve stimulation with implantable devices (even before the dorsal column stimulation, later known as spinal cord stimulation (SCS) was introduced), one of the eight patients with neuropathic pain presented with severe facial pain and had an electrode inserted deep into the infraorbital foramen; the stimulation resulted in lasting pain suppression as long as the stimulator was on [41]. Later, another patient had a system applied to the temporal area delivering stimulation aimed at the branches of mandibular nerve [46]. At about same time, Shelden implanted electrodes wrapped around the mandibular nerve itself and stimulated them in 3 patients through an implanted receiver at 14,000 Hz achieving temporary pain relief [29].

Based on the ''gate control theory'' of Melzack and Wall [19], PNS was used in multiple neurosurgical centers [2, 3, 12, 14, 15, 20, 21, 23, 25, 38, 40], and in most cases implantation involved surgical exploration of the peripheral nerve and placement of the flat plate (''paddle''-type) multi-contact electrode immediately next to it. Unfortunately, the reported results of PNS approach were not extremely encouraging in terms of pain relief. In addition to that, the reports of nerve injury from electrode insertion or stimulation-related fibrosis made PNS less attractive [11], particularly since the SCS approach became universally accepted as means of long-term treatment of medically intractable neuropathic pain of various etiologies. Few enthusiastic centers continued using PNS for certain neuropathic pain syndromes [6–8, 16, 27, 30, 36, 37, 42, 43], but the lack of wide interest among implanters resulted in little efforts from the device manufacturers in getting appropriate FDA approval for use of their implantable generators in PNS. Even now, according to the manufacturers' manuals, the only device specifically approved for peripheral nerve stimulation is a radiofrequency system made by Medtronic (Minneapolis, MN) while all other systems, including implantable pulse generators made by Medtronic, as well as devices made by Advanced Neuromodulation Systems (Plano, TX) and

Advanced Bionics (Sylmar, CA) are used for PNS on an ''off-label'' basis.

The use of PNS for craniofacial neuropathic pain was reborn in 1999 in publication of Weiner and Reed that described percutaneous technique of electrode insertion in the vicinity of the occipital nerves [44]. Soon after publication of that pioneer paper, we began using PNS approach in both occipital and trigeminal regions [31, 32]. Multiple other publications detailing experience of many centers followed over the next years [1, 4, 5, 9, 10, 16, 17, 24, 26, 28, 33–35, 45] with description of different techniques and applications.

Indications

The indications for PNS are quite specific: it is usually recommended for patents with neuropathic pain of various etiologies as long as there is some preservation of sensation in the area of pain. The four most common indications that have been described in the literature are (1) post-herpetic neuralgia involving territory of the trigeminal nerve; (2) post-traumatic or post-surgical neuropathic pain that is related to underlying dysfunction of the infraorbital, supraorbital, or occipital nerve; (3) ''transformed migraine'' presenting with occipital pain and discomfort; and (4) occipital neuralgia or cervicogenic occipital pain. In each of these situations, the patients have anatomical distribution of pain, their pain is medically intractable, they had favorable results of neuropsychological testing, the area of pain is not anesthetic (although hypoesthesia and hyperesthesia are allowed) and, in the first two groups, the onset of pain is linked to a certain traumatic, surgical or infectious event. In most places, a local anesthetic block is used to confirm involvement of the specific nerve into generation of pain, although elimination of pain with nerve block does not necessarily predict success of PNS. Therefore, a trial of stimulation is performed in order to check responsiveness of pain to the stimulation approach prior to the implantation of permanent system. Usually, a 50% improvement in pain intensity serves as a cutoff limit for considering the trial successful.

The psychological evaluation is routinely performed, at least in our practice, as it became a part of evaluation of all patients who are considered for pain-relieving surgery. Early detection of somatization, untreated depression, drug abuse and drug-seeking, as well as various secondary gains (not necessarily financial) that may not be obvious to the surgical team, help to predict success of surgery and address the issues that may negatively affect the outcome prior to the intervention.

The nerves that are most frequently selected for stimulation are supraorbital, infraorbital, less often auriculotemporal and supratrochlear, in cases of facial pain, and greater and lesser occipital nerves in cases of occipital pain. In our opinion, stimulating the nerve itself may be more effective comparing to the field stimulation, but this is debatable as those implanters who prefer field stimulation achieve very similar clinical results in terms of improvement and overall success.

Surgical procedure

The electrode(s) are inserted for the trial in sterile conditions either under local anesthesia or under sedation augmented by infiltration of the insertion site with local anesthetic. Since the procedure is short and the surgical site is quite superficial, general anesthesia is almost never needed.

The direction of electrode insertion may be chosen based on implanter's preference: we routinely insert electrodes from lateral to medial not only in the supraorbital and infraorbital regions (where it is probably the only way to put them) but also in the occipital area [35], whereas others prefer to insert electrodes from medial to lateral [1, 26]. Standard 4- or 8-contact electrodes are used; the electrodes are passed in the epifascial plane under the skin but above the muscles. Our general approach is to have the electrode cross the path of the nerve chosen as a stimulation target. As long as this nerve happens to be either under one of the electrode's contacts, or between two contacts, the stimulation can be steered toward it in order to get adequate coverage. For the trial insertion, we do not implant any deep anchors or extensions. The electrodes are sutured to the skin with plastic anchors and fine nylon, and a strain-relief loop is created around the insertion site to avoid inadvertent electrode pullout.

The electrodes are inserted under fluoroscopic guidance. Standard landmarks are used for the insertion – the supraorbital groove or foramen and the supraorbital ridge for the supraorbital nerve; the infraorbital foramen and the floor of the orbit for the infraorbital nerve (Fig. 1); C1 arch and radiographic midline for the occipital nerves (Fig. 2). In the beginning, we tested each patient for stimulation-induced paresthesias in the operating room so the position of the electrode could be adjusted if needed. Lately, however, we exclusively rely on anatomical electrode positioning due to its high reliability in getting appropriate coverage. This resulted in significant improvement in patient's comfort associated

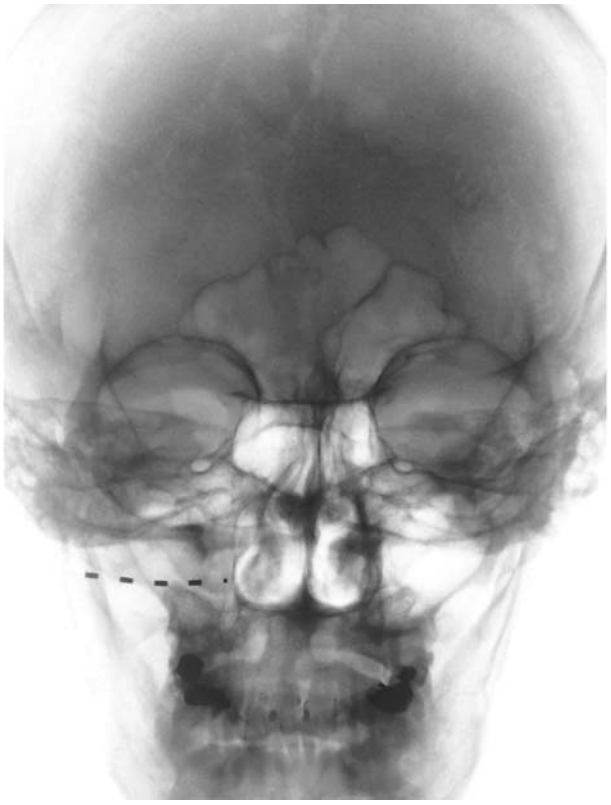

Fig. 1. Radiogram of infraorbital nerve stimulation electrode

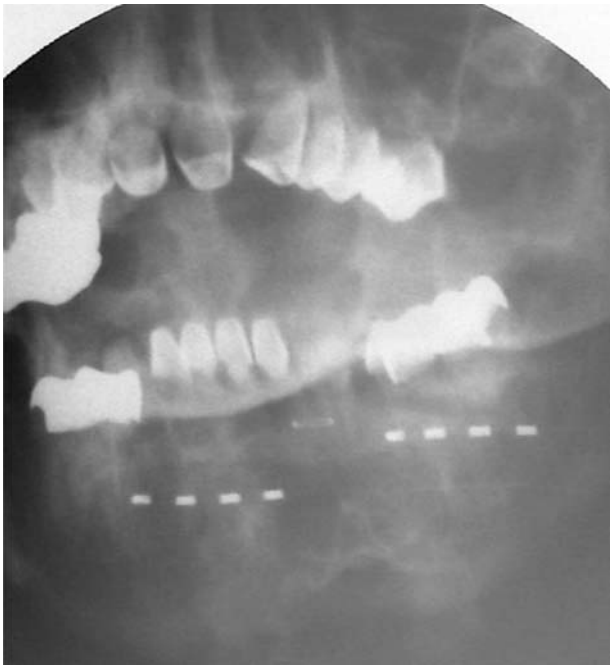

Fig. 2. Radiogram of bilateral occipital nerve stimulation electrodes

with deeper sedation that may be used now since the patient's cooperation is not needed. The electrode is covered with sterile dressing and attached to the external stimulation system; the initial programming is performed to produce adequate paresthesias in the painful area; the patient is instructed on adjustment of stimulator depending on activity and pain level; and antibiotics are prescribed for the duration of trial to avoid development of superficial infection (although this particular step is not supported by any clinical evidence).

Once the trial is completed, the temporary system is replaced with the permanent one. We prefer to remove the temporary electrode and then insert a brand new permanent electrode that is connected either directly to the generator or to an extension cable that connects to the generator. The electrodes that we use are cylindrical ''wire''-type (such as Quad, Octad, Quad Plus or Quad Compact, Medtronic; Qattrode, Octrode or Axxess, ANS; and Linear, Advanced Bionics). Other groups reported using ''plate''-type (''paddle''-type) electrodes (Resume, Resume II or Resume TL, Medtronic) for stimulation of occipital nerves. Implantation of such electrode may be preceded by a trial with ''wire''-type electrodes [10] or the trial may be done with ''plate''-type electrode connected to a temporary extension [24]. In all cases the electrodes are placed over the course of the peripheral nerve that supplies the painful area and may be involved in generation of pain.

The electrodes or extension cables are tunneled toward the generator pocket. The tunneling step is quite painful and necessitates the use of general anesthesia. Location of this pocket is chosen based on the patient's and surgeon's preference. Placement of generator into gluteal area [10, 28], abdominal wall [5, 44], or infraclavicular areas [9, 24, 33, 35, 44] has been described. In our opinion, infraclavicular area that is routinely used for placement of deep brain stimulation generators is preferred location for both trigeminal and occipital nerve stimulation systems. We recently analyzed experience of patients with infraclavicular generators and found extremely high level of their satisfaction with this particular location [39]. Independently of location, the pocket should satisfy certain requirements: it has to be deep enough to avoid hardware erosion; it should not be too deep to interfere with reprogramming or, in case of rechargeable devices, their regular charging; and it should be located in a relatively immobile region as the hardware may fail if subjected to repetitive mechanical stress.

Results

So far, all published reports on the use of peripheral nerve stimulation for control of neuropathic craniofacial

pain have shown significant and lasting improvement in pain intensity. Below, the published experience is reviewed based on treated diagnoses, although one has to keep in mind that the labeling painful conditions may be difficult at times.

The biggest group of patients suffered from occipital neuralgia and cervicogenic headaches. The pain in these patients is located primarily in the occipital region and the upper part of neck sometimes radiating toward the vertex or even the forehead. The occipital nerves that arise from upper cervical nerve roots participate in these pain syndromes and this participation is usually confirmed by the greater and lesser occipital nerve blocks. Weiner and Reed in 1999 reported improvement in all 13 patients with unilateral or bilateral occipital neuralgia that underwent occipital PNS implantation with average follow up of 2 years [44]. Later, same authors reported 80% success in a group of 62 patients with intractable occipital headaches [45]. Hammer and Doleys presented a patient with occipital neuralgia who was implanted with obliquely placed 8-contact electrode; she maintain 90% improvement in pain intensity as well as improvement in most psychological indicators [5]. Oh *et al.* described excellent and good outcome in 10 out of 10 patients with occipital neuralgia at 1 month follow up (>75% pain relief), but that effect persisted in 8 out of 10 at 6 month follow up [24]. Rodrigo-Royo *et al.* reported 3 patients with occipital pain and headaches and 1 patient with postherpetic occipital pain; all of them improved with occipital PNS and this improvement persisted till last follow up 4 to 16 months post-implantation [28]. Six patients with occipital neuralgia who underwent implantation of ''paddle''-type electrodes maintained significant improvement at 3-month follow up in a pilot study of Kapural *et al.* [10]. In our series, i.e. a group of 14 patients with occipital neuralgia, 10 patients exhibited improvement of pain during the trial and underwent implantation of a permanent system. The beneficial effect of chronic occipital PNS persisted in 80%, of those who significantly improved during the trial, over the follow up period of average of 22 months [35].

Another, potentially very common, indication for occipital PNS is the so-called transformed migraine. Migraine is a very common affliction, and frequently it is medically intractable. Recently, pain physicians started linking occipital neuralgia with ''spinally transformed migraine'' sometimes using these terms interchangeably [1]. Popeney and Aló reported results of occipital PNS in 25 patients with chronic disabling transformed migraine; at a mean follow up of 18 months improvement in migraine disability assessment score was almost 90% [26]. All 10 patients with severe chronic migraine who were used in a PET study of Matharu *et al.* achieved excellent pain relief with suboccipital stimulators (although one patient also required bilateral supraorbital stimulation) [17]. Whereas these two studies used percutaneous, ''wire''-type electrodes, Oh *et al.* reported 10 patients with transformed migraines that underwent implantation of ''paddle''-type electrode (7 of them had initially percutaneous electrodes that migrated and were replaced with surgical leads); all 10 had >75% pain relief both at 1 and 6 months after the implantation [24].

Indications for trigeminal branch stimulation are limited primarily to trigeminal neuropathic pain and postherpetic neuralgia. In one case, supraorbital stimulation was used in addition to bilateral occipital PNS for treatment of chronic migraine [17]. Treatment of postherpetic neuralgia involving the ophthalmic nerve distribution using PNS technique was first described by Dunteman in 2002; two patients had unilateral supraorbital PNS implants and maintained excellent pain relief for 3 years [4]. Johnson and Burchiel reported their results in 4 patients with postherpetic neuralgia affecting supraorbital region; 2 of these patients maintained >50% of pain relief after 2 years of follow up [9].

As to the post-traumatic or post-surgical neuropathic trigeminal pain, Burchiel reported more than 50% improvement in pain intensity in all patients who underwent permanent implantation of PNS system since 1998 [31, 32]. In a group of 6 of these patients, 1 failed to improve during the trial, and the remaining 5 maintained significant (>50%) improvement of pain with mean follow-up longer than 26 months [9]. We observed similar results; seven of 8 patients proceeded with implantation of permanent PNS system, one had the system removed 26 months later due to gradual loss of beneficial effects and the improvement in pain intensity, and the remaining 6 patients maintained 63–86% of pain improvement (a mean reduction of visual analog scale score of 74%) over 27.5 months of follow up [33]. In Burchiel's experience, out of 6 patients with non-herpetic trigeminal neuropathic pain, supraorbital and infraorbital distribution of pain was observed in 3 patients each [9]; in our patient cohort, 2 patients had infraorbital, 2 – unilateral supraorbital, and the remaining patients had bilateral supraorbital, unilateral infra- and supraorbital, unilateral infraorbital and occipital, and unilateral supraorbital and occipital pain.

Overall rate of complications was low; the majority of complications (wound breakdown, skin erosion, focal infections, discomfort due to short extension, etc.) were minor, and even if additional interventions were needed, none caused any serious or lasting problem.

As the experience with the use of PNS for craniofacial pain treatment grows, one may expect better definition of criteria predictive of lasting beneficial outcome. Publication of larger clinical series will likely result in wider acceptance of this treatment approach; its low invasiveness, testability, reversibility of effect and adjustability of settings may make it a preferred modality for otherwise intractable conditions.

The directions of future advances will also include development of neural prosthetic devices and hybrid bionic systems [22] and even less invasive single-channel and multi-channel micromodules [13]. Other targets, such as the vagal nerve, are also being investigated (and show some promise) for the treatment of chronic migraines and cluster headaches [18].

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Stimulation of the occipital nerve for the treatment of migraine: current state and future prospects

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Summary

Migraine is a common disabling malady. Despite the development of therapeutic agents such as the triptans, a significant number of patients continue to suffer. The evolution of peripheral nerve stimulation for headache management, may significantly improve the management of those who suffer from moderate to refractory migraine symptoms.

Keywords: Migraine; occipital nerve; neuromodulation; Bion®.

Introduction

Pain is the most common complaint that elicits a consultation with primary care physicians. The most common pain syndromes include headaches. It is estimated that 17% of the adult female population, 6% of the male population, and 5–10% of children suffer from migraine headaches. Migraine headache are most prevalent in the second to fourth decades of life, however a significant number of patients suffer from migraine headache after the age of 60 [16].

An accurate estimate of the economic impact of migraine headaches has been difficult to obtain. Most studies attribute the large economic burden to costs associated with decreased functional status and the consequent indirect cost to employers. Studies estimate that the average number of migraine attacks per year is 34 for men and 37.4 for women and that 58% of the attacks require bed rest. Moreover, annual medical treatment costs for migraine in the United States have been estimated to exceed 1 billion health care dollars. Female patients accounted for 80% of the total cost, physician office related expenses accounted for 60% of the total cost, and prescription drugs accounted for 30%. However, a surprising finding is the low cost of emergency department treatment for migraine headache which accounted for less than 1% of total cost. The cost of missed workdays and impaired performance because of migraine is estimated at $18 billion [16, 9].

Several studies revealed that the majority of patients with migraine headache remain undiagnosed and untreated. It is estimated that half of all patients that meet the International Headache Society (HIS) criteria for migraine headache remain undiagnosed [9]. A recent study by Sheftell *et al.* identified several barriers for care including identifying migraine sufferers in need of care as not all headache patients may need care, improving medical recognition, improving medical diagnosis, improving medical confidence, improving migraine treatment, and assessing treatment outcomes [14].

Patients that end up with chronic daily headache or chronic daily migraine tend to be very refractory and resistant to treatment. A three-year retrospective study conducted in 271 patients had their headaches diagnosed as either, chronic daily headache, episodic tension type, episodic migraine or mixed headache. These patients sought other types of treatment and in this instance Botulinum toxin type A due to the fact that 77% were refractory to oral medications and 48% had overused their medications during a migraine attack [4].

Another study by Bigal *et al.* indicated important differences in the relative frequency of chronic daily headache (CDH) subtypes among adolescents and adults. The study indicated that transformed migraine (TM) accounts for 69% of CDH in the adolescent population, in comparison to 87% in adults. These results are broadly compared with other studies from US headache centers, which report that most adults with CDH have TM.

Results of this study indicated that medication overuse is an important factor as it was present in 71.5% of adults and 41% of adolescents [3].

In general, patients with comorbid medical or neurological illness are often more difficult to treat. Several comorbid diseases have been associated with migraine patients with a greater frequency as would be expected by chance alone. Migraine is associated with depression, anxiety disorders, clinical and sub clinical brain lesions and other types of chronic pain. Moreover, these patients

Table 1. *Acute treatment of migraine attacks*

Drug/dose	Level of evidence	Scientific data	Clinical impression	Adverse effects
Chlorpromazine 0.1–1 mg/kg IM 12.5–37.5 mg IV	+/++	++	++	++
Metoclopramide 10 mg IM, 20 mg PR 0.1 mg/kg to 10 mg IV	++	+/++	+/++	+/−
Prochlorperazine 10 mg IM/IV, 25 mg PR	++	+++	IV > IM > PR	++
Butalbital/aspirin/caffeine	+	−	+++	+/−
Plus codeine	++	++	+++	+/−
DHE ± antiemetics 1 mg IM/IV/SC	++	++/+++	+++	+++
DHE nasal spray	+++	+++	+++	+++
Ergotamine ± caffeine	++	+	++	+++
Ketorolac IM 30–60 mg	++	+	++	−−
Aspirin 500–1000 mg Ibuprofen 400–2400 mg Naproxen sodium 750–1250 mg	+++	++	++	−−
Diclofenac potassium 50–100 mg Flurbiprofen 100–300 mg Naproxen 750–1250 mg Piroxicam 40 mg	++	+/++	++	−−
AAC	+++	+++	++	+/−
Butorphanol nasal spray Acetaminophen plus codeine Parenteral opiates	++/+++	++/+++	++/+++	+++
Sumatriptan Intranasal, oral, SC Rizatriptan Zolmitriptan	+++	+++	+++	++
Naratriptan	+++	++	++	++
Dexamethasone IV	+	+	++	+/−
Isometheptene and combinations	++	+	++	+/−
Lidocaine intranasal	++	++	−−	++

IM Intramuscular; *IV* intravenous; *PR* rectally; *DHE* dihydroergotamine; *AAC* acetaminophen, aspirin and caffeine; *SC* subcutaneous.
Level of evidence: +++ Consistent evidence from multiple randomized clinical trials that is relevant to the recommendation, ++ randomized, clinical trials support the recommendation however, the evidence was not optimal. For example there were few trials, evidence was inconsistent or the patient population was different from the target patient population, + no relevant randomized clinical trials exist. *Scientific data*: 0 The medication is ineffective or harmful, + the effect of the medication is either not statistically or clinically significant, ++ the effect of the medication is statistically significant and exceeds the minimally clinically significant benefit, +++ the effect is statistically significant and far exceeds the minimally clinically significant benefit. *Clinical impression*: 0 Ineffective: most people gain no improvement, + somewhat effective: few people gain clinically significant improvement, ++ effective: some people gain clinically significant improvement, +++ very effective: most people gain clinically significant improvement.

Table 2. *Preventative treatment of migraine*

Drug/daily dose	Level of evidence	Scientific data	Clinical impression	Adverse effects
Clonidine/guanfecine	++	+/−	−−	+/−
Carbamazepine 600 mg	++	++	−−	+/++
Divalproex sodium Sodium valproate 500–1500 mg	+++	+++	+++	+/++
Gabapentin	++	++	++	+/++
Topiramate	+	−−	++	++
Amitriptyline 25–150 mg	+++	+++	+++	+++
Nortriptyline	+	−−	+++	+++
Protriptyline Doxepin Imipramine	+	−−	+/++	+++
Fluoxetine	++	+	+	+
Fluvoxamine Paroxetine Sertraline	+	−−	−−	+
Phenelzine	+	−−	+++	+++
Other antidepressants	+	−−	+	+
Propranolol	+++	++	+++	+/−
Timolol	+++	+++	++	+/−
Atenolol Metoprolol Nadolol	++	+/++	++/+++	+/−
Diltiazem Verapamil Nimodipine	++	+/−	+/−	+/++
Methylergonovine	+	−−	+	+++
Methysergide	+++	+++	+++	+++

Level of evidence: +++ Consistent evidence from multiple randomized clinical trials that is relevant to the recommendation, ++ randomized, clinical trials support the recommendation however, the evidence was not optimal. For example there were few trials, evidence was inconsistent or the patient population was different from the target patient population, + no relevant randomized clinical trials exist. *Scientific data*: 0 The medication is ineffective or harmful, + the effect of the medication is either not statistically or clinically significant, ++ the effect of the medication is statistically significant and exceeds the minimally clinically significant benefit, +++ the effect is statistically significant and far exceeds the minimally clinically significant benefit. *Clinical impression*: 0 Ineffective: most people gain no improvement, + somewhat effective: few people gain clinically significant improvement, ++ effective: some people gain clinically significant improvement, +++ very effective: most people gain clinically significant improvement.

are more likely to have a negative cardiovascular risk profile and to have certain congenital heart defects such as patent foramen ovale [13].

Several treatment options are now available for migraine headache; however, effective management of migraine headache should incorporate a multidisciplinary approach. Recently, evidence-based, multispecialty, consensus guidelines were developed by the US Headache Consortium in an effort to enhance the care of migraine patients and their recommendations will be outlined. Evidence-based guidelines for headache management were released in 2000 by the US Headache Consortium (USHC), which was made up of a multidisciplinary panel of professional organizations. The main goal was to establish treatment guidelines in four distinct areas of migraine management: diagnostic testing, pharmacological management of acute attacks, preventive therapy, and behavioral and physical treatments of migraine. Levels of evidence, quality of evidence, scientific effect measure, and clinical impression of effect scales and the recommendations for the acute and preventive treatment of migraine headache will be outlined in Tables 1 and 2 [15].

Occipital nerve stimulation

Evolution of occipital nerve stimulation (ONS) as a therapeutic alternative for migraine, reflects an extension of traditional peripheral nerve stimulation for neuropathic

pain states. The linkage of the occipital nerves and headaches, begins with appreciation of the neuroanatomic pathways between the upper cervical nerve roots of C1–C3 and the trigeminal nerve nuclei. It is by means of these anatomic connections the physiologic event of convergence occurs.

Understanding of the trigeminal-cervical [7] pathways has contributed to interventional management of headaches. Procedures such as occipital nerve blocks, C2–C3 facet procedures, C2 selective nerve blocks as well as their associated neurolytic interventions have significant utility for acute headaches with dwindling relief in the chronic setting.

Bartsch and Goadsby [1] have illustrated the clinical importance of trigeminal-cervical pathways through a series of animal models, which explain the impact of occipital nerve stimulation on the trigeminal pathways and vice versa. Understanding these interrelationships, is critical to transforming basic science into a sound therapeutic rational for ONS as a therapy for refractory migraine patients.

The earliest coherent history of this therapy begins with Weiner's [18] original paper, which displayed how a group of headache patients underwent treatment with neuromodulation, via a percutaneous approach. The therapeutic implications of this new treatment reflected a therapy paradigm shift. More importantly, Dr. Weiner's preliminary data suggested the potential to develop a new management scheme for these challenging headache patients.

A review of the current literature shows the number of published case series and technical papers for ONS is small and represents the infancy of this therapy. The outline below of published reports is a good representation of the current evolutionary trends of this new treatment.

1999 Weiner *et al.*, Peripheral neurostimulation for the control of intractable occipital neuralgia.

2000 Weiner, The future of peripheral nerve stimulation [17].

2003 Dodick, Occipital nerve stimulation for chronic cluster headache [6].
Popeney *et al.*, Peripheral neurostimulation for the treatment of chronic disabling, transformed migraine [12].

2004 Matharu *et al.*, Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study [10].
Oh *et al.*, Peripheral nerve stimulation for the treatment of occipital neuralgia and Transformed Migraine using a C1-2-3 subcutaneous paddle style electrode: a technical report [11].

2005 Kapura *et al.*, Occipital nerve electrical stimulation via the midline approach and subcutaneous surgical leads for treatment of severe occipital neuralgia [8].

These articles are not complete representations of the literature of ONS therapy from 1999 to 2005. During that time there were many associated abstracts and oral presentations, but these case series and technical reports represent the essence of this therapy.

During the earliest phase of ONS, trials and resulting implantations, were based upon the preliminary diagnosis of occipital neuralgia. A suggestion of the potential for success was a positive response to neural blockade. Thus, the therapeutic course mirrored the traditional algorithm for peripheral nerve stimulation for neuropathic pain.

Evolution of this therapy followed two significant events. The first consisted of trialing and implantation of patients who had failed medical and interventional measures, with significant positive responses. The second consisted of evaluation of a group of Dr. Weiner's patients by PET scan. This proved that 8/10 occipital neuralgia patients had migraine, as well as a potential central scheme for pain relief. As a result of the PET scan study, the peripheral and central elements of ONS as well as their neurophysiologic implications are readily appreciated.

The current literature of technical case series, explores the typical range of diagnoses treated with this therapy:

1. Occipital neuralgia
2. Cervicogenic headache
3. Transformed migraine

Patient selection

Treating the refractory patient begins with ascertaining the fitness of this intervention for the individual. The preliminary inclusion and exclusion principles are essentially identical to traditional neuromodulation implantation selection schemes used in peripheral nerve and spinal cord stimulation. These decisive factors include, defined diagnosis, refractoriness to conservative therapy, absence of addiction, absence of psychological contraindications or tissue related causes such as infections at the site of proposed trial or implant.

Defining refractoriness is complex, given the infancy of this therapy. A unified standard for ''treatment refractory'' patients has yet to develop. Personal experience as well as the literature [5] has demonstrated that patients

with migraine may have a significant response to interventional measures. Thus, any guidelines for treatment failure may have to be inclusive of failure to medical and interventional therapies. This definition will have greater clarity as we define where this therapy fits into the current therapeutic scheme for management of these difficult patients.

Understanding this therapy requires a detailed description of its component step from patient selections to final implant. This author's (LLR) implantation practice begins with trialing and implanting only patients who are under the care of a neurologist with subspecialty expertise in headache. This author finds this has contributed to the long-term success of patients by ensuring optimal pre-implant evaluation with proper diagnosis. In addition, the continued availability of ideal medical management throughout all phases of this therapy facilitates the most favorable outcomes.

This author begins evaluation of the medical patient with a systematic review of the checklist outlined below. This checklist represents the various phases of the plan. These include, preliminary evaluation, trial, implant or both trial and implant.

The primary concern before a trial of these patients, is to explore suitable non-surgical choices that may provide long-term relief of the patient's presenting symptoms. A special concern is the issue of pregnancy and neuromodulation. A significant number of the women evaluated are of childbearing age. The pulse generators used have never undergone evaluation in pregnancy, for obvious ethical reasons, and thus potentially represent a relative contraindication to those seeking to become pregnant. Cyberonics® (Vagal nerve stimulation) has received post market approval for the use of their pulse generator in pregnancy, with no complications in the small patients series followed.

Checklist

1. Treatment refractory (medical), absence of contraindications
2. Evaluate for response to interventional therapies (decide if a cervicogenic component is present)
3. Behavioral medicine evaluation
4. Absence of medical contraindications
5. Trial; I use an operating room, several environments may be acceptable.
6. Surgical approach
   - Medial vs. Lateral (lead)
   - Prone vs. Lateral
7. Lead type
   - Cylindrical vs. Paddle style
   - Four electrodes vs. Eight electrodes
8. Number of Leads
   - Unilateral vs. Bilateral
9. Trial period
   - Five–seven days
10. Anchoring mechanism
11. Pulse generator
    - Non-rechargeable vs. rechargeable
    - Placement site
    - Size
12. Soft cervical collar
    - Trial and implant
13. Stimulation parameters
14. Defining success

Headache patterns

Few if any of the published literature on ONS provides any visual representation of the presenting headache patterns of these implanted patients. In this authors practice experience, several distinct anatomic patterns benefit from this therapy:

C2 pattern (unilateral or bilateral): Radiation from Occiput to vertex/frontal region and vice versa. May include peri/retro-orbital pain. Unilateral vs. bilateral presentation.

Frontal pattern: Bilateral vs. unilateral.

Holocranial: No dominant side, often have significant component involving the vertex.

Surgical technique

Anesthesia for the procedure typically consists of moderate sedation, to facilitate patient-implanter communication and lessen the risk associated with a sedated patient in the prone or lateral position, with poor access because of the surgical field. This author has used ketamine as a primary or adjunctive agent during the implant, because of marked analgesia with preservation of spontaneous respiration.

Most of the ONS literature describes Weiner's technique to position the leads at (C1–C2). None of the implant techniques described in the literature provide any hint of the difficulty or the time frame needed to gain satisfactory paresthesias in the typical patient. A review of the literature, with respect to the occipital nerve anatomy [2], indicates it can be found 5–28 from the midline on either side, along the intermastoid line.

I perform the procedure using the midline, to approach the C1–C2 and the intermastoid levels under fluoroscopy. The intermastoid approach provides an advantage in readily locating the occipital nerve, at this author's experience; neither technique provides a significant advantage. The intermastoid line approach could have significant utility for practitioners early in their experience.

Lead placement via the curved Tuohy needle, is improved with, proper curvature of the needle mirroring the occiput, as well as placing the needle in the midportion of the subcutaneous tissue. To ease ideal needle placement, I create a small incision (for trials) down to the subcutaneous tissue. Rapid placement of the leads with as few passes as possible results in the best stimulation patterns. Paresthesias radiating to the vertex at low amplitude will improve the trial. The ideal lead for this therapy has not been determined as of yet. Cylindrical leads are problematic due to the frequency with which migration occurs. Until this issue is resolved, we cannot address the issue of whether any particular lead type adds specific benefits based on the individual patient characteristics.

The question of whether to place unilateral versus bilateral leads has not been fully clarified. Typically 6–16% of migraines tend to be ''side-locked''. The current literature demonstrates several cases of unilateral lead placement returning for lead placement on the contralateral side. This is similar to my own experience. Reevaluating these cases, it was clear it would have been technically easier, and cost-effective to implant bilateral leads in all patients with unilateral headache patterns.

Securing the leads in place with the supplied anchor is helpful to minimize the risk of suboptimal trial by lead displacement. The anchors supplied with all the implanting kits are challenging for this procedure. The anchor I have had the most success with has been the Twistlock (Medtronic Corp). The feature that improves this anchor is the twist lock feature that consistently grips the lead with the same amount of force irrespective of operator skill. This removes one maneuver required to secure the leads. The limitation of this anchor is the size and hardness.

Lead migration

Anchors and anchoring mechanisms have become an important part of the discussion, and evolution of this therapy. Migration rates in the current literature have been in the 30–50% range with the cylindrical leads. The resulting frustration has caused some practitioners to abandon the technique; in addition the migration issues resulted in changing the technique using surgical paddle style leads. Thus far, there has been no migration with these leads. The difficulty with paddle lead is the increased dissection needed at the occiput.

I have experienced few migrations with implants over the years. I credit that to use of the Twistlock anchor, creating two strain loops (one in the occiput and a second at the electrode/extension level T1–T2). In addition all patients are required to wear a soft collar to minimize neck mobility during the trial and implant. After the implant patients, are required to wear the soft collar for six weeks.

Within a week of definitive implantation, I refer patients to a physical therapist (who understands the implantation process). The goals of this single session were to gradually extend the thoracic loop, which is not anchored by suture. During this time, the therapist teaches the patients how to limit their cervical range of motion. The overall benefit is reduction of stress to the leads, and decreased episodes of lead disruption with loss of paresthesias.

Recently, I have explored using small profile silicone anchors with silicone glues. In conjunction with the glue, three nylon sutures were applied around the anchor. A single suture to secure the lead and anchor together after the Silicone glue has been applied; two more sutures are used to secure the lead/anchor unit to the tissue.

Trial period

The trial period is variable with experiences extending from on the table trials to seven days for most practitioners. Concerns of infection are one reason that decides the length of the trial for many practitioners.

The impact of the trial period has not been clarified. Clearly those patients with ideal responses undergo a successful trial in a short period of time. My current anecdotal experience suggests that roughly 10–15% of patient's do not gain any satisfactory clinical response during the trial. On the contrary anecdotal experience suggests that many patients experience progressive improvement in their responses after implantation. This clinical experience is suggestible that some patients may display an optimal therapeutic response to an extended trial period.

Soft collar

Using a soft collar is not universal among implanting doctors. I have used soft collars on all my patients for

trial and implant. The goals were to reduce motion of the hypermobile neck with a simple reminder, and promote lead scarring without disruption.

Since the collar is not used in a uniform fashion, and the implanter skill variable levels and lead securing techniques are inconsistent, the impact of the soft collar is unclear for the implant population as a whole.

Pulse generator

The most recent evolution in pulse generators has brought rechargeable, smaller size and the ability to steer the current more effectively. The small size (Advanced Bionics) and rechargeability are the features that impacted my implant experience. Many of my implanted patients were young women, despite their significant debilitation; aesthetics and repeat surgical procedures were of concern. Patients who had reviewed the choices through self-education and direct questions to me often chose a rechargeable pulse generator. To date, all major neuromodulation companies have a rechargeable power source.

As this field matures, the ideal patient selection may include determining whether any of the unique elements of the various commercially available pulse generators offer any specific advantages.

Stimulation parameters

Stimulation parameters are quite broad within the current ONS literature. Table 3 represents the wide range of the variables encountered. The absence of physiological parameters that can be readily followed in response to the therapeutic effect, probably contributes to the relatively extensive range of these variables.

Prior to the availability of rechargeable pulse generators, programming represented a balance between ''optimal'' stimulation patterns versus preservation of the implantable pulse generator (IPG) lifespan. The advent of these new IPG's facilitates focusing on the parameters best suited for the individual patient.

Defining success

The most critical element of the trial process is a goal-oriented determination of what should be considered a successful outcome for the patient and physician. This can be the challenging element of this process because the individual characteristic of each patient may not lend himself or herself to a singular acceptable outcome scheme.

Table 3. *Stimulation parameters in ONS*

Pulse width (msec)	Amplitude (volt)	Pulse rate (Hz)
90–400	0.5–8.5	55–130

Most of the migraine patients implanted by this author have continued to use their migraine medications, and what has mainly changed has been the degree of use. Many patients have had a marked drop in their medication requirements, which were suboptimal, and now have increased efficacy. The current literature does not clarify the nature of the post-implant relationship between patient and their medical headache specialist.

Evolving this therapy will require that we define whether it is a stand-alone versus adjunctive therapy. I would anticipate that based on the experience with the vagal nerve stimulators for epilepsy and depression, the latter will be most likely. In that regard the medical headache practitioner must continue to be a critical part of the therapeutic team post implantation.

The future of occipital nerve stimulation

Occipital nerve stimulation has evolved as a therapy with the introduction of the Bion Microstimulator, (Advanced Bionics Corp. Sylma California), Figs. 1 and 2. This new microstimulator is a self-contained device with a rechargeable battery. The Bion measures 27 mm in length and 3 mm in diameter. The absence of leads reduces the risk of migration and fracture. The absence of leads potentially enables patients to return to full activity with essentially no restrictions (personal experience 13 patients, LLR).

One of the most important attributes of the Bion is the possibility of a single stage procedure, i.e. in those patients who respond to the initial implant the ''trial''

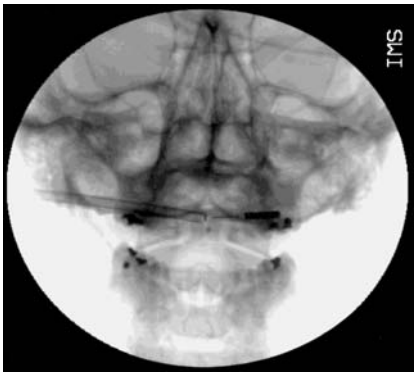

Fig. 1. Bion and introducer

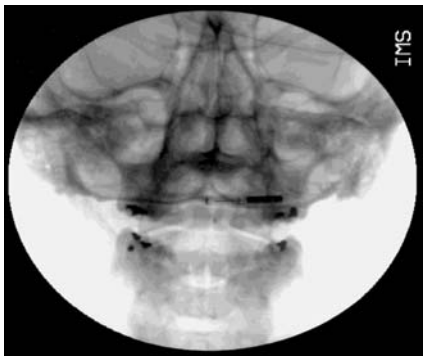

Fig. 2. Bion deployed

becomes the definitive implant with no further interventions. Implantation time was also quick. Surgical time ranged from 15 to 30 minutes in most cases.

The Bion is monopolar and is placed in proximity to the Occipital nerve via a percutaneous approach using specialized tools and an injection tool. The minimally invasive injection approach resulted in rapid recovery after the procedure during the preliminary feasibility study.

The preliminary feasibility study implants were all unilateral. The intermastoid line was the major anatomic landmark. Along this line the occipital nerve was readily found using a nerve stimulator incorporated into the Bion deployment tool. Patients were extremely receptive to this device due its miniature form. Preliminary evaluation of the therapeutic response is promising and the greatest obstacle was the unanticipated need for patients to undergo excessive charging. Nonetheless, many patients would repeat the experience. The Bion is in its next phase of development and it is anticipated that this power source issue will be resolved. Future Bion development may also facilitate the utilization of this device at earlier stages with anticipated improved outcome.

The evolution of the Bion may well change the point at which we can introduce neuromodulation into the routine management of headache. The ability to extend ''state of the art'' medical therapy in conjunction with early neuromodulation therapy may change the rate at which transformed migraine occurs in this population.

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Occipital neurostimulation for treatment of intractable headache syndromes

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Summary

Intractable migraine and other headache syndromes affect almost 40 million Americans and many more millions worldwide. Although many treatment protocols exist, mainly designed around medication regimens, there are estimated to be at least 3–5% of these headache sufferers that do not respond in a meaningful way to medications and whose lives can be severely restricted to darkened, quiet rooms, heavy doses of narcotics, failed personal relationships and an overwhelming sense of hopelessness. In this article, we describe current neuromodulation-based approach to the management of intractable headache.

Keywords: Neuromodulation; migraine; headache; occipital neuralgia; occipital neurostimulation; chronic benign pain.

Introduction

Primary headache disorders are a dominant presentation in many neurology and primary care practices worldwide. A greater understanding of the various headache types has been facilitated by the recent reclassification scheme developed by the International Headache Society (IHS) in 2004 [5]. Clarification of the diagnosis criteria for various migraine and tension headache syndromes, as well as, the addition of previously unrecognized conditions such as hemicrania continua and a more precise definition of secondary headaches such as occipital neuralgia are extremely important in the formulation of successful treatment strategies by the clinician.

Intractable migraine, cervicogenic, and secondary headache syndromes such as occipital neuralgia, affect almost 40 million Americans and many more millions worldwide [12]. It is estimated that up to 5% of these headache sufferers experience daily or near daily headaches (transformed migraine, chronic daily headaches) and 1–2% are so poorly responsive to medication paradigms that this failure can lead to narcotic dependence, severe restrictions in daily activities, failed personal and career objectives and an overwhelming sense of hopelessness and despair.

Neuromodulation for treatment of chronic pain disorders over the past 35 years has centered on spinal cord (dorsal column) and peripheral nerve stimulation using implanted electrode and generator devices to modulate perception of abnormal pain signals to the brain. More recently [15] it has been reported that successful neuromodulation for occipital headache syndromes can be accomplished with subcutaneous regional electrode placement at or near the level of C1 without direct contact with a specific peripheral nerve.

Literature

Occipital nerve neurolysis and/or neurectomy have been part of the neurosurgical armamentarium in treating intractable occipital headaches for many years. Though occasionally very effective, the not infrequent development of delayed deafferentation pain in the distribution of the affected occipital nerve limits the long-term usefulness of the procedure. C2 ganglionectomy [7] in posttraumatic C2 pain syndromes has resulted in an 80% good to excellent outcome with a 3-year follow-up. Non-traumatic C2 pain patients did not fair nearly as well and subtle but significant morbidity including postoperative dizziness or gait disturbances may be a persistent problem.

C2 nerve decompression [11] can achieve up to a 79% success rate with 33% pain free and 46% adequate pain relief over 2 years. C1, 2 fusion [6] can correct focal instability and may be indicated on occasion. C1-3 posterior rhizotomy [3] via ventrolateral DREZ lesioning at

C1-3 can be an effective but highly invasive surgical technique. Neurolysis of the greater occipital nerve [2, 8] can be effective in the short run but most patients tend to have significant recurrences within one to two years. Picaza *et al.* [10] reported pain suppression by peripheral nerve stimulation on six patients with occipital neuralgia using a cuff electrode technique with 50% good outcome. Waisbrod *et al.* [13] reported a very good result from stimulation of the greater occipital nerve for painful peripheral neuropathy.

Experience with peripheral nerve electrical stimulation for painful mononeuropathies and complex regional pain syndromes involving major peripheral nerves led to the sentinel observation by the author that subcutaneous tissue can conduct and propagate electrical impulses in a dermatomal and/or myotomal distribution of one or more peripheral nerves without direct nerve contact producing pain relief in the region of the electrically induced local paresthesias. This has led to the development and refinement of a percutaneous neurostimulation procedure implanted transversely into the subcutaneous space nominally at or just above the level of C1 [14, 15] as a minimally invasive treatment alternative for intractable occipital headache syndromes.

Beginning in late 1992, the author began implanting percutaneous wire electrodes in a series of patients with refractory occipital headaches felt to be unresponsive to medication but with excellent if temporary response to occipital nerve steroid/anesthetic block. All patients underwent successful percutaneous trial stimulation for up to seven days prior to permanent implant and had acceptable behavioral and psychological profiling.

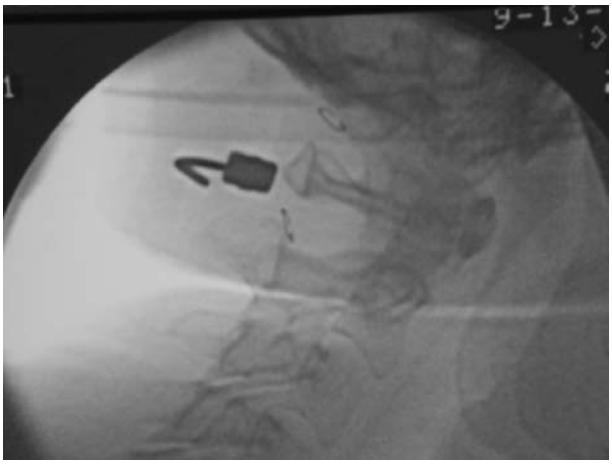

Fig. 1. Needle localization

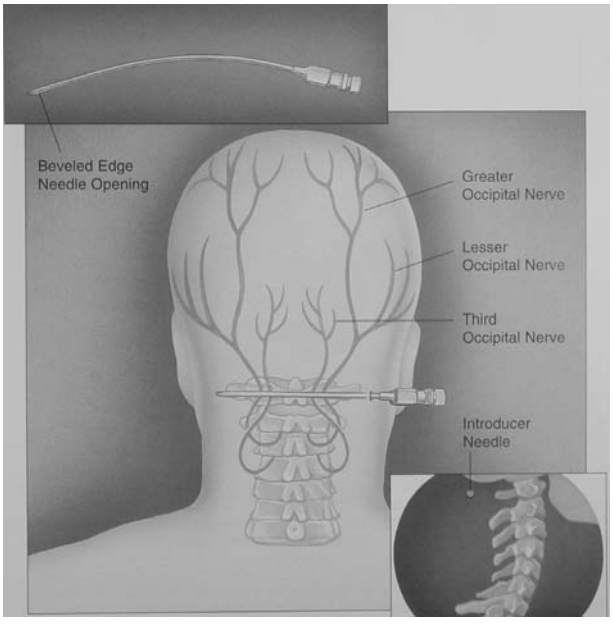

Fig. 2. Curved needle placement

Surgical technique

Using local anesthesia at the incision site only, a vertical 2 cm incision is made at the level of the C1 lamina either medial and inferior to the mastoid process or in the midline posteriorly under fluoroscopic control (Fig. 1) extending to but not into the cervicodorsal fascia. The patient may be positioned laterally or prone depending on the incision entry point. The subcutaneous tissues immediately lateral to the incision are undermined sharply to accept a loop of electrode created after placement and tunneling to prevent electrode migration. A Tuohy needle is gently curved to conform to the transverse posterior cervical curvature (bevel concave) and without further dissection is passed transversely in the subcutaneous space across the base of the affected grater and/or lesser occipital nerves which at the level of C1 are located within the cervical musculature and overlying fascia (Fig. 2). Single or dual quadripolar or octapolar electrodes may be passed from a midline incision to either affected side or alternatively placed to traverse the entire cervical curvature bilaterally from a single side or via two opposing incisions.

Rapid needle insertion usually obviates the need for even a short acting general anesthetic once the surgeon becomes facile with the technique. Following placement of the electrode into the Tuohy needle, the needle is

withdrawn and the electrode connected to an extender cable for intraoperative testing.

Intra-operative stimulation testing

After lead placement, stimulation is applied using a temporary RF transmitter to various select electrode combinations enabling the patient to report on the table the stimulation location, intensity and overall sensation. Most patients have reported an immediate stimulation in the selected occipital nerve distribution with voltage settings from 1 to 4 volts with midrange pulse widths and frequencies. A report of burning pain or muscle pulling should alert the surgeon the electrode is probably placed either too close to the fascia, intramuscularly, or too far above or below the C1 level and should be repositioned. Repeated needle passage for electrode placement can lead to subcutaneous edema and/or hematoma formation with loss of electrode conductivity thereby blocking evaluation for permanent lead positioning.

Surgical paddle electrodes can also be implanted subcutaneously, though somewhat more invasively, using sharp dissection techniques with the electrode contacts oriented towards the fascia [9].

Electrode fixation and tunneling

Probably the most important aspect of the procedure involves techniques to prevent electrode migration (pull-back) from its transverse subcutaneous position in the highly mobile upper cervical region. Following successful stimulation, the electrode is sutured to the underlying fascia with the supplied silicone fastener and 2-0 silk sutures. A small dab of medical grade silicone glue is placed between the fastener and electrode using a small angiocath to ensure fixation. A loop of electrode (Fig. 3) is also sutured loosely in the previously prepared subcutaneous pocket to reduce migration risk as well. A short acting general anesthetic is used to tunnel the electrode(s) or extender wire to the distal site for connection and implantation of the receiver or generator.

Pulse generator implantation

There are two options available for the system power source: an external radiofrequency (RF) transmitter/receiver system, or an implantable pulse generator. The RF system allows for more continuous higher voltage outputs at the expense of rechargeable 9-volt batteries and is FDA approved for peripheral use. Most patients, however, opt for the implantable pulse generator system which is currently an off-labeled application for peripheral use. With the voltage settings usually required for occipital stimulation, the lithium ion battery can last 3–5 years before replacement. In the past year, rechargeable generator systems designed for long-term use even with high voltage requirements have become available.

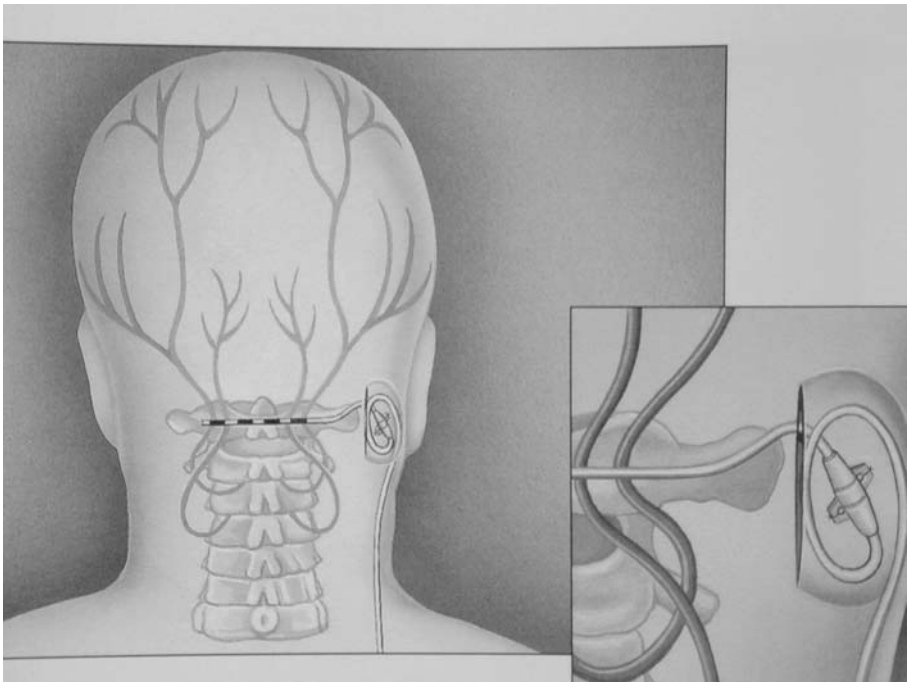

Fig. 3. Electrode anchoring position with loop strain relief

Generator placement appears to influence both patient positioning during the procedure and the risk of postoperative migration. Typical implant locations are:

1. Upper buttock – facilitates single stage electrode and generator placement in the prone position.
2. Abdomen – usually done with the patient in the lateral position.
3. Upper chest – lateral or supine positions favor this location.

There is significant extension wire stretching with upper buttock generator placement when a patient bends forward creating excessive tugging on the cervically placed electrodes. This could be one of the major factors, along with anchoring technique, mitigating electrode migration. Thus, abdominal or anterior chest placement might reduce the risk of migration.

Results

Implant experience from 1993 through 2005 has consistently shown an approximately 75% good and excellent long term pain relief with a 15% fair and 10% poor response in over 150 implanted patients with long term follow-up. The total headache years in this population was approximately 1200 years with mean headache duration of 8 years in 77% females and 23% males. Most of the patient population exhibited some degree of bilateral pain with one side typically dominant. Preoperative Visual Analogue Scale (VAS) scores ranged from 5 to 10 with a mean of 9. Postoperative VAS ranged 0–6 with a mean of 3.

Stimulation usage

Patients report using the devices in a variety of scenarios including intermittent stimulation for migraine with aura, cervicogenic headache, occipital neuralgia, post herpetic neuralgia, tension headache and cluster headaches. Continuous use with chronic daily headaches (transformed migraine) and even deafferentation posttraumatic pain is common as well.

Complications

Most complications have revolved around lead migration (15%) skewed more towards the early years of implant technique development. Improved anchors and anchoring techniques as well as continuing education opportunities for implanter should minimize this concern. Generator placement and future development of localized leads and minigenerators should also have a positive impact on reducing or even eliminating migration problems. Lead breakage or disconnection (8%) is probably a function of the lead implant location in a highly mobile area. Infection was relatively uncommon (3%), however, attention to meticulous surgical technique is essential to avoid primary contamination of the implanted equipment even from skin contaminants such as staphylococcus epidermidis. Subsequent wound dehiscence with external exposure of any of the implant requires explantation of the total device. In our experience, a previously infected area can be successfully re-implanted after suitable treatment.

Positioning and sedation

Most electrode implants can be performed in the lateral position utilizing a midline incision for bilateral electrode placement with lead tunneling and generator pocketing either in the chest, upper buttock or abdomen. This allows greater access to the airway during short-acting sedation.

Surgical paddle placement, especially bilaterally, is facilitated in the prone position on a horseshoe or similar frame, however, airway access is limited and sedation agents should be chosen that do not significantly alter respiration (i.e. ketamine, etc).

Mechanism of action

The mechanisms of action for the paresthesia patterns and pain relief obtained from this therapy are incompletely understood but would appear to involve the following elements:

- Subcutaneous electrical conduction
- Dermatomal stimulation
- Myotomal stimulation
- Sympathetic stimulation
- Local blood flow alteration
- Peripheral nerve stimulation
- Peripheral and central neurochemical mechanisms
- Trigeminovascular system

The most important of these mechanisms appears to be the trigeminovascular system.

In the cat, direct electrical stimulation of the greater occipital nerve [4] increased the metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn cells by 220% ipsilaterally to the stimulation and by a lesser amount contralaterally. The dorsal horn activity was at the level of C1, C2 and interaction with the trigeminal innervated structures suggests that the frontally radiating occipital headaches occur as a consequence of overlap of nociceptive information processing at the level of the second order neurons. PET scan studies in episodic migraine headache patients [1] demonstrate specific areas of brainstem activation in the dorsal rostral pons. A PET study of 8 patients with chronic migraine headaches [8], that showed excellent responses to implanted bilateral suboccipital stimulators, also demonstrated activation of the dorsal rostral pons that persisted after alleviation of headache pain. These observations suggest the presence of a central trigger mechanism for a variety of headache pain conditions. Peripheral, subcutaneous electrical stimulation may influence blood flow within these activated regions or be involved in descending pathways that control pain via stimulation of the trigeminovascular system at the level of the upper cervical spine.

Conclusions

Peripheral subcutaneous neurostimulation for a variety of intractable headache syndromes is a safe, reasonably effective, and uncomplicated treatment modality to be considered when dealing with patients refractory to medications and other non-invasive treatment options. Multicenter studies are underway to further define the safety and efficacy of this treatment modality. Competition among the device companies will allow development of more compact and appropriate implant hardware to maximize the treatment potential.

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Spasticity and related disorders

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The phenomenon of spasticity: a pathophysiological and clinical introduction to neuromodulation therapies

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Summary

Spasticity is part of the complex clinical picture which results from the upper motor neuron impairment. The underlying mechanisms that produce the automatic overactivity of the muscle groups may manifest themselves as either passive movements dependent on the exerted velocity or persistent muscle overactivity in the form of spastic dystonia. The therapeutic management of spasticity is closely related to the aims of rehabilitation; these include avoidance of complications, restoration of movement, re-education of motion and gait, development of self-dependency, and social integration, as well as modification and reorganization of the cortical brain map. The latter is achieved through long-term learning processes which are subserved by new neurophysiological dynamics, and the mechanisms of neuroplasticity which develop during neural regeneration.

Keywords: Spasticity; hypertonia; upper motor neuron syndrome; rehabilitation; neurophysiology; neuroanatomy; neuromodulation.

Definition and clinical considerations

Spasticity has been known as a manifestation of nervous system malfunction for a long time and, the term ''spasticity'' has been given various definitions [19, 20]. Lance, in 1980, provided perhaps the most appropriate definition for spasticity [11] as ''a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (''muscle tone'') with exaggerated tendon jerks, resulting from hyperexcitability of the tonic stretch reflex, as a component of the upper motor neuron syndrome''. Other scientists defined spasticity as the only manifestation of upper motor neuron impairment, which responds to medical treatment [15]. Few years later, Young introduced the clinical entity ''spastic paresis'' [23]; this included extensor plantar responses, velocity-dependent increase in tonic stretch reflexes, exaggerated phasic stretch reflexes, increased autonomic reflexes, and abnormal postures. Spasticity is considered a sensorimotor phenomenon, associated with automatic movement responses to sensory inputs. Spasticity increases the velocity of the existing passive muscle stretch and is also related with changes occurring in the spinal cord. Diffuse injuries in the central nervous system (CNS) result in loss of descending inhibitory commands and abnormal impulses. Muscle activity becomes overactive. This is mediated at several areas of the stretch-reflex pathway. Loss of descending inhibitory (reticulospinal) influences leads to exaggerated excitability of dynamic gamma neurons and alpha motor neurons. Other spinal tracts such as the vestibulospinal and rubrospinal tracts become more active. Essentially, spasticity can result from injury to the cortex, basal ganglia, thalamus, brainstem, cerebellum, central white matter, or spinal cord [10].

In cases of spasticity, the resistance to passive movement is highest at the beginning of motion, while it attenuates as the applied pressure increases. This is evidence of motor pathway impairment that deranges the voluntary motion; it also produces marked increase in muscle tone, as well as restriction of the motion range or profound rigidity of the limbs. As a result, abnormal postures become apparent due to antagonist muscle overactivity. Noticeably, the level of increased muscle tone among the antagonist muscles differs in the various joints, particularly when the brain or spinal cord damage is focal or incomplete. In contrary, when diffuse or global lesions of the brain or spinal cord take place, the spasticity is much more homogeneous. The above discrepancies may be related to the specific characteristics

of the damage itself (i.e. location, extension etc) or to the positive or negative activity of agonist and antagonist muscles. More specifically, in incomplete lesions, the agonist muscles are able to partially or totally overcome the increased muscle tone of the antagonist muscles. The complete loss of agonist muscle strength enhances the overactivity of the antagonist muscles, which are in a spastic condition, and may lead to abnormal limb postures, frequently of permanent character (co-contractions). When both agonist and antagonist muscle groups have been activated (co-activation), another type of abnormal motion ensues. Therefore, in both cases, the possibility for voluntary movement is lowered and the resulting motional actions have an abnormal, non-functional character [13].

The role of agonist muscles in the expression of the pathological motional response has been recently recognized, particularly after the advent of therapeutic modalities for the treatment of focal or generalized spasticity and the evolution of advanced rehabilitation methods. The bedside measurements of spasticity by manipulations of the passive motion differ considerably when compared to the estimations during a voluntary motion, in sitting or standing position or during walking. During the functional evaluation of spasticity in a patient suffering from CNS damage, apart from the increased muscle tone, a range of atypical movements in terms of abnormal reflexes may also be present. Automatic plantar extensor responses, clonus, synergias, co-contractions or synkinesias associated reactions (Fig. 1) can be such paradigms. These may produce abnormal patterns of posture, motion and gait such as typical arm posture in hemiplegic patients or characteristic spastic gait following incomplete spinal cord injuries. The pattern of motion, however, is critically influenced by other factors such as the disturbance of equilibrium and coordination, the impairment of nociceptive sensory pathways, the function of autonomous nervous system and fatigue (Fig. 2).

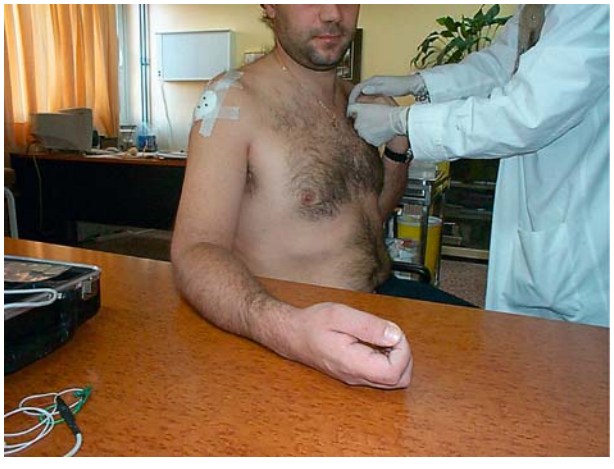

Fig. 1. The maximum resistance of the not affected arm produces automatic contractions of the homonymous muscle of the hemiplegic side (associated reactions)

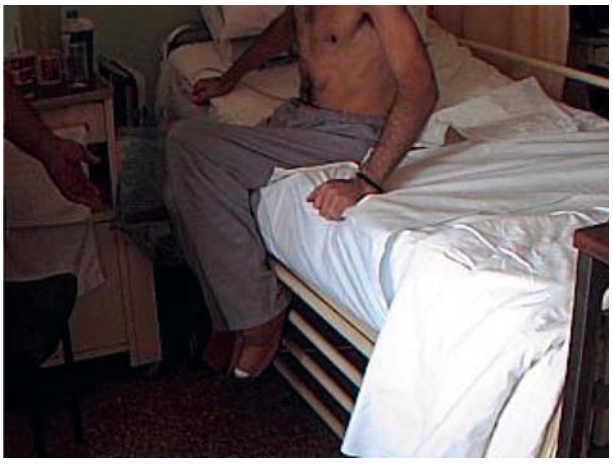

Fig. 2. When the paraplegic patient is sitting, massive, automatic motions of the trunk and lower limbs are produced with obvious risk of falling down

Although spasticity constitutes only one clinical aspect of the upper motor neuron syndrome (UMNS), it dominates the pathogenesis of abnormal motion; moreover, it may set off a series of other relevant clinical findings. For example, the local injection of Botulinum toxin Type A (BTX-A) into the flexor muscles of a paretic arm may induce both reduction of focal spasticity and improvement of motion not only in the hemiplegic arm but also in the distal limb; this is nicely illustrated in the case of synkinesias described in hemiplegic patients during walking. Therefore, the management of spasticity enables the sufferer to be re-educated in his body posture, motion, gait, and nociceptive function, in order to modify other immature elements caused by CNS damage. Such kinds of symptoms are the stereotypic, massive, and synergistic movements, which, however, do not result in a functional motion. Overall, the clinical presentation of a CNS lesion is mainly characterized by spasticity and the patient may be identified as a spastic individual.

Taking together the aforementioned definitions and descriptions, it becomes obvious that the clinical manifestations occurring after a CNS lesion are poorly understood. These could be clarified only on the basis of their pathophysiological profile and clinical expression. For this aim, the USA National Institutes of Health spon-

sored an interdisciplinary workshop in 2001 to define the terms spasticity, dystonia, and rigidity [18]. It was concluded that *spasticity* is hypertonia combined with either of the following findings: a) resistance to an externally imposed movement that increases with increasing speed of stretch and varies with the direction of joint movement or b) resistance to externally imposed movement that increases above a threshold speed or a joint's range of angle. The term *dystonia* refers to involuntary, sustained or intermittent muscle contractions, which cause twisting, repetitive movements, or abnormal postures [18]. Finally, *rigidity* corresponds to the hypertonic condition in which all of the following are true: (a) resistance to externally imposed joint movement is present at very low speeds of movement, does not depend on imposed speed, and does not exhibit a speed or angle threshold; (b) simultaneous co-contraction of agonists and antagonists may occur, and this is reflected by the immediate resistance to a reversal of the direction of movement about a joint; (c) voluntary activity in distant muscle groups does not lead to involuntary movements about the rigid joints, although rigidity may worsen; and (d) the limb does not tend to return to a particular fixed posture or extreme joint angle [18]. Despite the consensus on the above definitions, the diagnostic approach to such clinical syndromes may reveal other ambiguous neurological conditions, in which less clearly defined symptoms are present or different movement disorders coexist. For example, the term *cogwheel rigidity* describes the condition in which tremor is superimposed on muscle stiffness [4]. *Spastic dystonia* has been another such a paradigm; the term describes the relative inability to rest of a muscle that is responsive to the degree and duration of the tonic stretch imposed on the muscle. Finally, the term *spastic cocontraction* implies the simultaneous activity of both agonist and antagonist muscle groups; although it is commonly present in normal movements [12, 21], it is excessively profound in spastic paresis [6].

Upper motor neuron syndrome (UMNS)

The upper motor neuron (UMN) lesion is characterized by both positive and negative phenomena (Table 1), which differ in their pathophysiological basis and respond variably to treatment. The *positive* phenomena are ''phenomena of presence'' of involuntary focal or generalized muscle overactivity and expressions of a generalized movement disorder. Their manifestation is sudden, unforeseeable, and characterized by intense

Table 1. *The positive and negative findings of upper motor neuron syndrome (UMNS)*

Positive findings	Negative findings
Spasticity	Loss of dexterity
Spastic dystonia	Atrophy
Dystonia	Loss of coordination
Clonus	Loss of voluntary movement
Athetosis	Muscle weakness
Primary reflexes	Fatigue
Babinski sign	
Rigidity	
Synergias	
Co-contractions	
Synkinesias	
Associated contractions	
Myelic automatisms	

symptoms. The *negative* phenomena are ''phenomena of absence'', reflect the inability of voluntary movement (i.e. muscle hypoactivity), resist to treatment, and result in a more severe neurological disorder [5].

Pathophysiology of spasticity

In human, the UMN lesion affects both the pyramidal and corticospinal tracts. When these pathways are impaired, increased irritability of the a-motor neuron at specific spinal myelotomes appears; this results in increases in both the muscle tone and responsiveness of the corresponding tendon reflex. Many of these phenomena can be understood in terms of the muscle spindle

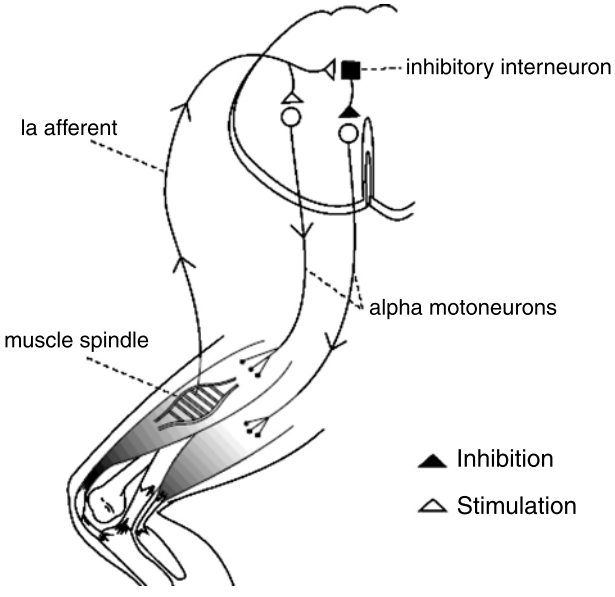

Fig. 3. The model of the afferent-efferent neural circuit in stretch reflex activity

physiology. Initially, the afferent intrafusal Ia fibers of the muscle spindle are irritated by muscle stretch, and create a monosynaptic augmenting connection to the a-motor neuron of the muscle; however, they are also linked with the a-motor neuron of the antagonist muscle. When the muscle strains, simultaneous activity of the stimulated synergistic a-motor neuron and the inhibited antagonist muscle results to nociceptive inhibition (Fig. 3). In UMN lesion, this disequilibrium of excitation-inhibition affects the executive organ of motion, i.e. the muscle. On this ground, someone may consider spasticity as a motor phenomenon guided primarily by sensitivity.

Obviously, the neurogenic model of disturbance between afferent and efferent stimuli of the stretch reflex implies a disequilibrium of muscle activity at the joint level; in particular, the agonist muscles overact voluntarily while the antagonist muscles remain inert. In UMN lesions, positive and negative signs coexist in a single joint and in adjacent joints; this results in paradox stereotypic movements, which are not integrated towards performing an intended movement. The overactivity observed in agonist muscles may be attributed to the following two factors: a) subsequent sprouting, and b) mechanisms of plastic neural rearrangement [2, 9, 14]. Notably, the above mechanisms of spasticity need considerable time to evolve. On the other hand, the hypoactivity present in antagonist muscles may be caused by: a) the cerebral or spinal shock, b) the main lesion, and c) additional separate lesions in the peripheral nervous system. The disequilibrium in muscle activity in specific joints is better understood in cases of cerebral damage such as stroke [8].

Spasticity and neurological recovery or maturation

Spasticity does not develop immediately after an acquired or congenital lesion; instead, a period of loose paralysis precedes spasticity which lasts variably depending on whether the spinal cord or the brain have been affected. The development of involuntary muscle overactivity may be regarded as a CNS recovery process, which follows a lesion and is integrated in mechanisms of plasticity or neural regeneration. Synaptic plasticity and neural sprouting appear when a lesion interrupts the descending fibers at a level above the brain stem. When the interrupted descending fibers degenerate, adaptive sprouting occurs locally. Plasticity-related changes result to long-term abnormal automatic responses to peripheral stimuli as in the case of skin irritation or muscle strain [7, 16, 17, 22].

Apart from the intermediate neurons, adaptive sprouting may also be observed in the nearest intact descending pathways. In late stages of recovery, other mechanisms are also implicated such as the reorganization of higher centers in order to recruit new mechanisms of movement response. These processes are integrated via intact descending pathways of the brain stem such the rubrospinal, reticulospinal, and tectospinal tracts. The aforementioned associations to the spinal motor neurons may be more diffuse and less selective compared to the corticospinal pathways. The reorganization of the descending tracts may also involve branches of corticospinal fibers, which have survived and innervate irrelevant groups of motor neurons. These mechanisms cause abnormal activation of the supraspinal descending fibers, which results in muscle overactivity; however, the degree of coordination of normal movement is adequate for integrating a purposeful action [3].

In animal experiments, it was shown that the local spinal reorganization may lead to new forms of behavior such as novel myoskeletal expression of gait or new pattern of urination [17]. In incomplete lesions, the high degree of spasticity along with the involuntary massive movements that occur during the purposely effort to perform a specific action, mostly superimpose any voluntary movement. In such cases, the disequilibrium between agonist and antagonist muscles is more important and spasticity appears earlier and is more intense. Weakness and inactivity succeed muscle hyperactivity around a specific joint; these decrease muscle elasticity and cause degeneration of the muscle fibers and finally, hyperflexion of the joint.

Effects of spasticity on the soft tissues and functional performance

When a cerebral or spinal lesion occurs suddenly, a period of flaccid paresis precedes the positive signs of UMNS and spasticity. During this phase, the negative phenomena of UMNS (loss of muscle activity) dominate the clinical presentation. This flaccid phase is attributed to neuropraxia and may last up to one month in cases of cerebral damage or up to several months, in spinal cord lesions (‘‘spinal shock’’). During this flaccid phase, gravity is the only force exerted on the inert muscles and joints leading thus to paradox postures such as foot drop (Fig. 4). If not properly treated, these sequeale influence the muscle elasticity and permanently affect the mass of the muscle and its adjacent tendons. The emergence of spasticity signals the transition to an ad-

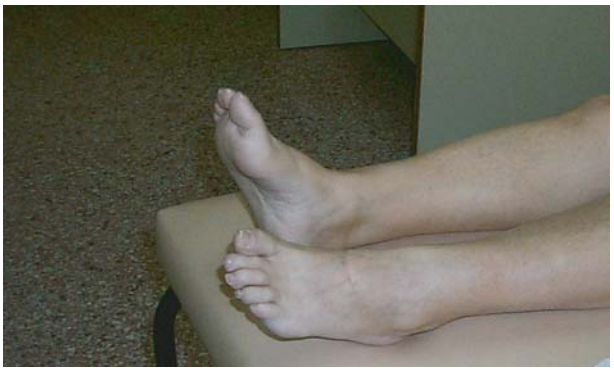

Fig. 4. There is marked foot drop in the left hemiplegic side, given that gravity is the only force exerting on the inactive muscles

vanced phase of neurological ''recovery''. In incomplete lesions, this period may last for a long time whereas, after complete lesions, it terminates once automatic movements appear. Following a brain injury, the automatic movements are massive, gross, and paradox due to intervening synergies, synkinesias, and other associated reactions. After the spinal shock, spontaneous movements appear in parts of the body that receive input from myelotomes located below the level of the spinal cord injury.

Once the first signs of spasticity appear, their intensity increases progressively to reach a state of permanent involuntary muscle overactivity, even though the individual may lie quietly. This phenomenon is defined as *spastic dystonia* and produces paradox postures of the body depending on the groups of muscles that overact. The typical arm posture of a hemiplegic patient is a characteristic paradigm of spastic dystonia (Fig. 5). Similarly, in brain injury, the clinical picture includes arm adduction, flexion and internal rotation of the elbow and wrist and finger flexion. The involuntary muscle overactivity is characterized by increase in recruited motor units and difficulty in halting the activity of certain motor units during either the resting phase or when other muscle groups are normally activated. This condition may be defined as an ''early spastic state'', in which soft tissues remain elastic while findings of fibrosis, muscle shortening or cocontractions in the joints have not become apparent yet. When further changes in soft tissues occur, the continuous stimuli either augment or reproduce the spasticity; this, in turn, leads to further abnormal postures of the limbs and cocontractions. The above condition of positive feedback between spasticity and muscle alterations is defined as ''late spastic state''. The soft tissue alterations lead to resistance to movement independently of the velocity and along with spasticity make passive movements difficult and slow; moreover, the range of motion in affected joints is limited. When such a pathological condition is prolonged, significant joint deformations, abnormal body posture, and pathological patterns of motion or gait are expected to appear in due course. The existing modifications of soft tissues result in further structural alterations of the affected muscle and tendons; the subsequent fibrosis and reduction of muscle compliance limit substantially the range of joint motion (Fig. 6).

The term *hypertonia* refers to the clinical condition in which the range of movement is critically limited due to both spasticity and decreased muscle and tendon elasticity. Hypertonia is one of the negative sequelae of UMN

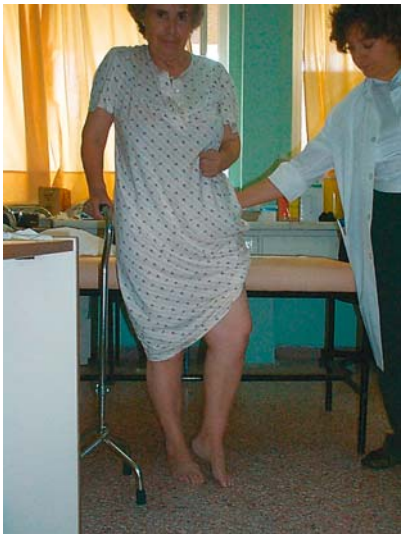

Fig. 5. Patient presenting with hemiplegia and typical arm posture

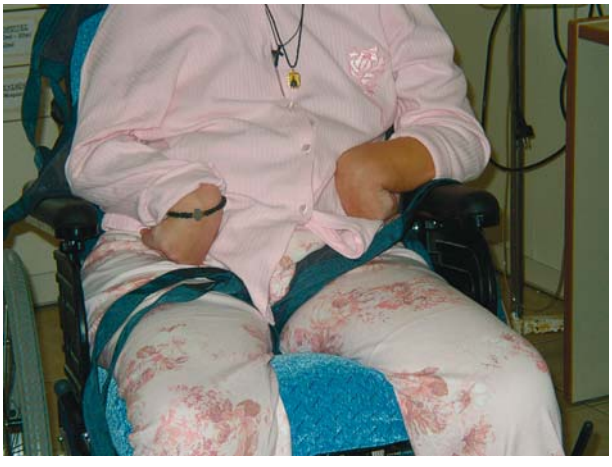

Fig. 6. High degree of spasticity in both upper limbs following a severe head injury. Permanent deformities and co-contractions are apparent

lesion; the failure to offer timely the appropriate treatment has been the major etiologic factor for this incapacitating condition. The superimposed complications deteriorate the existing spasticity and the resultant positive feedback of abnormal sequelae affect critically the functional capability of the sufferer. The joint deformation is caused by: a) spastic dystonia, b) soft tissues degeneration, and c) antagonist muscle weakness, irrespectively of whether paresis or atrophy has produced it. At this stage, cocontractions and/or abnormal body posture may be reversed by appropriate conservative or surgical interventions. If treatment is denied or fails to improve these conditions, focal bone deformations ensue. In severe or complete CNS lesions, the positive signs of UMN damage are generalized below the level of injury and affect both agonist and antagonist muscle groups. In this condition, the patient appears stiff, his joints are motionless, while trunk, upper and lower limbs may be functionally indiscriminate. Pain, sleep disorders, difficulty in swallowing, respiratory distress, decreased control of sphincters, inability to sit or stand comfortably, ulcers decibutus, and inflammations are among the other common complications of severe UMN lesion.

Models of spasticity

Spinal cord lesion model

Herman and colleagues [8] demonstrated that, in cerebral lesions, maximal reflex responses follow a few cycles of gastrocnemius muscle stretch. In contrast, in patients with spinal cord lesions, there is a late increase in tendon reflexes when the gastrocnemius muscle is repeatedly stretched. The above late response was attributed to the gradual and augmentative transmission of the stretch stimuli via intermediate neurons. A spinal cord lesion causes disinhibition of the local multisynaptic pathways; as a result, the afferent impulses originating from the muscle spindle are transmitted to the intermediate neurons via multisynaptic chains. In spinal cord lesions, centripetal activity, which originates from muscle spindle or tendon reflex afferents, enters the spinal cord at a specific myelotome but spreads uninhibited both in caudal and cephalad directions; this causes massive motor response from several muscle groups, even if only a single pathway was originally affected. For example, when the first sacral (S_1) root is irritated in a paraplegic patient's foot, then, knee flexion (5th lumbar root), hip flexion (2nd lumbar root) and abdominal muscle contractions (10th thoracic root) are observed. Although the flexor responses dominate in spinal cord lesions, augmentative stimuli are frequently transmitted from the flexors to the extensors musles as well.

Cerebral lesion model

Herman [8] observed that, in patients suffering from cerebral palsy, a quick motor response follows the rhythmic stretch of the gastrocnemius muscle; this implies that the initial stimuli is transmitted via a monosynaptic pathway. Clinically, this type of spasticity appears as a typical arm posture, in which antigravity muscles overact. In particular, shoulder abduction, elbow and wrist flexion are prominent in upper limbs, while hip abduction, knee extension and plantar flexion prevail in lower limbs [14]. During passive movement examination, the antigravity muscles appear spastic, but it is not clear whether this reflects an abnormal driving of peripheral stimuli to the spinal circuits or results from inappropriate centripetal signals. In patients with cerebral palsy, the interruption of the dorsal tracts does not inhibit the antigravity character of spasticity. Cerebral and spinal lesions of the CNS have different clinical presentations which depend on the mechanism of injury (traumatic versus nosological), the extension and the location of the damage, the involvement of either one or both cerebral hemispheres, and the impairment of higher cognitive functions. The negative phenomena of spasticity appear and are influenced by whether the patient participates in adjunctive treatments. In hemiplegic patients who actively participate in their rehabilitation program, there is much better development of movement ability in both the healthy and affected side of the body. When an intensive educational program is followed from the early days of the disease, spasticity bears much lesser consequences. The cognitive involvement and the body perception through nociceptive mechanisms greatly affect the primary clinical presentation of spasticity and the efficacy of the applied adjunctive treatment.

Conclusions

Extended clinical studies have shown that spasticity is not a static phenomenon but changes over the course of the day and during the months or even years that follow the CNS insults; moreover, it is clearly affected from external factors and stimuli (sensory, auditory, visual, etc). Therefore, the management of spasticity requires a deeper knowledge of its fluctuating and progressing dynamics, as well as an effective approach through cog-

nitive and educational processes. An integrated rehabilitation program, apart from the management of spasticity, should also aim to exploit the increased muscle tone to the advantage of functionality. This is a long-term therapeutic process in which the sufferer re-learns new approaches to its body functions and is supported to integrate them again in his/her personal and social life. In cerebral lesions, the management of spasticity and the reeducation of the patient in activities of daily living provide the brain with augmentative signals, which motivate mechanisms of plasticity and neurological recovery. This interaction between spasticity management and brain function constitutes the theoretical base where ''neuromodulation'' can be applied. In incomplete spinal cord lesions, the management of spasticity enhances the residual abilities of motion and practically guides the neurological recovery. Additionally, in spinal cord lesions, the improvement of spasticity clearly improves everyday quality of life in terms of reduced complications, better use of functional orthoses, functional reeducation, and greater performance in self-dependency scores [1]. The management of spasticity should be incorporated in all neurorehabilitation programs; this practically aims to create a satisfactory pattern of body posture and motion and improve substantially the functional capabilities of the patient. The reorganization of the cerebral cortex or spinal cord constitutes long-term targets of an effective neurorehabilitation program.

Neuromodulation of spasticity: future directions

It is clear that the pathogenesis of spasticity involves many different components. Future putative neuromodulatory interventions, therefore, should take into consideration a number of issues such as:

a) if sensitivity is a key factor, the role of epidural spinal cord stimulation (SCS) or peripheral nerve stimulation (PNS) could be greater than what is currently acknowledged and should be explored with appropriate research protocols
b) if reorganization of higher (i.e. cortical) circuits is important, the role of either motor cortex or sensory cortex stimulation could be important
c) in the past, the cerebellar stimulation has been applied in the treatment of spasticity in patients suffering from cerebral palsy; in view of current advances in neuromodulation, its role should be re-examined
d) the role of deep brain stimulation (DBS) in the treatment of spasticity of cerebral origin should also be explored
e) the value of combinations of chemical treatments (baclofen) with neurostimulatory treatments should be investigated
f) the classification of the various clinicoanatomical profiles (types) of spasticity should be refined and become more precise.

Finally, a better understanding of the evolution of spasticity may improve the timing of our interventions and clarify whether earlier administration of established treatments such as intrathecal baclofen can result to even better neuronal reorganization and adaptive responses.

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Intrathecal baclofen in current neuromodulatory practice: established indications and emerging applications

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Summary

Intrathecal baclofen (ITB) has evolved into a standard treatment for severe spasticity of both spinal and cerebral origin. The accumulated promising data from reported series of patients receiving ITB therapy together with the fact that spastic hypertonia commonly coexists with other neurological disorders have constituted a solid basis for offering this kind of treatment to patients suffering from other movement disorders. These include motor disorders such as dystonia, amyotrophic lateral sclerosis, status dystonicus, Hallervorden-Spatz disease, Freidreich's ataxia, ''stiff-man'' syndrome, but also vegetative states after severe brain trauma, anoxic encephalopathy or other pathology and more recently, various chronic pain syndromes. In this article, on the basis of the established applications of ITB therapy, we review the important emerging indications of this rewarding neuromodulation method and attempt to identify its future potential beneficial role in other chronic and otherwise refractory neurological disorders.

Keywords: Neuromodulation; spasticity; hypertonia; pain; intrathecal baclofen therapy; spinal injury; head injury; multiple sclerosis; cerebral palsy; vegetative state.

Introduction

Baclofen, a derivative of diazepam, was originally developed in the 1920s as an anticonvulsant. Over the next decades, its role in controlling epileptic fits proved to be limited but its potent action in alleviating spasticity of cerebral or spinal origin was noted. Pharmacologically, baclofen is a structural analog of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA), binding specifically on b receptor subtype [35, 65, 97]. Baclofen exerts its effect at the presynaptic level, where it reduces the excitability of motor neurons inhibiting the release of excitatory neurotransmitters; hence, high-frequency motor output and reflexively mediated muscle activity (i.e. spastic motor activity) are attenuated [19].

Oral administration of baclofen has been shown to be an effective treatment for motor disabilities due to spasticity; however, when higher doses of the drug need to be administered in order to suppress symptoms of hypertonia, untoward systemic effects may be produced. These effects include drowsiness, confusion, lethargy, and muscle weakness and may outweigh the expected benefit from the treatment. To avoid such unacceptable sequelae, baclofen was infused in the intrathecal space via a spinal tap; a dramatic improvement in severity of spasticity signs was achieved at significantly lower doses of the drug. The difficulty in administering intrathecal baclofen (ITB) by lumbar puncture on a regular basis was overcome when fully implantable drug-delivery devices became available in the 1980s. Over the past 20 years, the biotechnology industry has produced a series of advanced, sophisticated pumps which achieve to infuse drugs, including baclofen, intrathecally in a constant, continuous, reversible and fully telemetrically adjustable manner via an external programming device operated by a physician or other health professional.

ITB therapy has gained a steady foothold in the management of spasticity regardless of its underlying pathology. However, the range of neurological disorders that might improve by ITB therapy is steadily increasing; combinations of neuromodulatory interventions are tried clinically by experienced scientific groups and new indications are added in the relevant list of this treatment. In the present article, the established applications of ITB treatment in current neuromodulatory practice are reviewed in brief, while the future directions of the field are outlined.

Pathophysiological and clinical considerations of ITB therapy for spasticity

Pathophysiological background

Baclofen binds to presynaptic GABA-b receptors at any location along the neural axis i.e. cerebral cortex, white matter, brainstem, and particularly, dorsal horns of the spinal myelotomes [2]. Due to the hydrophilic nature of the drug, oral doses of baclofen result in limited absorption into the cerebrospinal fluid (CSF). Notably, ITB therapy shows two inherent advantages compared to oral administration of the drug: a) when given intrathecally, baclofen results in drug levels in CSF 10 times greater that those found following an oral dose 100 times larger [21, 69] and b) despite the high concentration of baclofen in the CSF of the lumbar region, it is only ¼ of that concentration that is detected in the cisterns of the brain [42, 43, 77]. However, adverse effects of general central nervous system (CNS) depression, albeit uncommon, may still appear following ITB administration; these include ataxia, somnolence, sedation with tolerance, suppression of the cardiovascular function, and sudden respiratory arrest [21]. Overall, the key element of effectiveness of ITB therapy is the high concentration of the drug around the tissues most responsible for the spasticity, i.e. the spinal cord, with little exposure of the brainstem and cerebrum; this allows excellent lower body spasticity control without the sedating unwanted effects that are associated with oral doses of the medication.

Clinical considerations – inclusion criteria

ITB has evolved into a standard treatment for severe spasticity of both spinal and cerebral origin. Spasticity is a motor disorder characterized by a ''velocity-dependent increase in tonic reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflexes'' [45]. Although spasticity constitutes only one component of the upper motor neuron syndrome (UMNS), it actually dominates the pathogenesis of abnormal motion, clearly interfering with co-existing incapacitating neurological symptoms, i.e. released flexor reflexes, weakness and loss of dexterity [53, 71]. Spasticity has a dramatic impact on both the functional capacity and quality of life of sufferers. Patients experience muscle contractures, joint deformities, painful spasms, skin breakdown secondary to shearing, while their functional mobility and self-dependency are substantially reduced. Moreover, spasticity is associated with lower respiratory function secondary to deformities, difficulty with hygiene in specific areas (e.g. palm or groin), deranged speech and swallowing, decreased ambulation and transfer capability, difficulty in seating, depression, increased risk of urinary infection and autonomic dysreflexia, as well as sexual dysfunction.

Spasticity is produced by a variety of pathologies affecting either the brain or the spinal cord. Any lesion in the spinal cord [e.g. trauma, myelitis, or multiple sclerosis (MS)] can interrupt the descending inhibitory signals, which balance the excitatory afferent impulses reaching the α-motoneuron. On the other hand, a damaged brain due to stroke, cerebral palsy, MS or head injury may be unable to generate the inhibitory signals necessary for controlling muscle tone and body motion. Taking into account the clinical diversity of various pathologies interfering with spasticity, it is of mandatory importance to select among all sufferers from spastic hypertonia those who have better chances to improve following continuous ITB therapy. Francisco described the perfect ITB candidate as one who has had ''a stroke with severe, functionally limiting, multijoint spastic hypertonia and predominant involvement of the lower limbs, and one who can neither tolerate the effects of oral drugs nor respond to adequate doses of other therapies'' [30]. The explicit criteria for considering candidates for ITB treatment are severe spasticity, clinical stability, age greater than 4 years, and body size sufficient to support the implantable device. On the other hand, explicit contraindications for this type of therapy include allergy to oral baclofen, active infection, and pregnancy. During the pre-implantation period, it is very important for health professionals, patients and caregivers to understand that ITB does not constitute the first choice of treatment for reducing signs of spasticity nor can cure the underlying pathology. Conversely, all alternative treatments including oral medications, local injections of botulinum toxin A (BTX-A) or phenol, and physical modalities should be tried first and have either failed or provided limited spasticity control. Furthermore, sufferers, family members and care providers should have realistic and obtainable goals and be motivated and committed to a demanding and long-term support and follow-up.

As the effect of ITB may be unpredictable, an infusion lumbar test is performed in each patient who is a potential candidate for this kind of intervention [11, 59, 60]. In this way, attending physicians, patients and caregivers can judge not only the efficacy of the drug but also the safety of the procedure before a final decision is taken to implant a permanent indwelling pump. A single dose of 50–150 mg baclofen is infused through a spinal tap and

the effect in spastic symptoms and functional performance of the patient is evaluated at 30 min, 4, 12, and 24 h later. This may be repeated 1 to 2 days later if the first test did not provide conclusive results. It is generally accepted that subjects are considered suitable candidates for continuous ITB therapy if, after baclofen screening test dose, a reduction in Ashworth scale [7, 16] or Penn Spasm Frequency Scale [69] by 2 or more points, for at least 6 hours, is documented without the development of untoward effects [59, 60]. Moreover, the functional capability of the patient is recorded for 24 hours post-trial; any change in wheelchair seating, gait, transfers, speech, bowel and bladder management, and ease or speed of locomotion are carefully evaluated [8].

ITB therapy in current neuromodulatory practice

Established applications

Clinically, spasticity may develop following damage at any level of the central nervous system (CNS) i.e. cerebral cortex, basal ganglia, thalamus, brainstem, cerebellum, central white matter, or spinal cord [40]. Therefore, the indications of ITB vary according to the underlying pathology; such pathologies include mainly spinal cord injury, multiple sclerosis (MS), cerebral palsy (CP), stroke, and head injury [23, 93].

Since 1984, when Penn and Kroin first infused baclofen intrathecally for treating spasticity [67], ITB therapy has increasingly gained a primary role in the alleviation of this incapacitating neurological disorder. Lower limb spasticity of spinal origin was the first indication of ITB and the largest published series include, in most part, patients suffering from spinal cord injury or MS [36, 55, 56, 66, 68, 69, 72, 96]. The promising results obtained from ITB therapy in patients suffering from spasticity of spinal origin urged neuroscientists to offer this kind of treatment in individuals suffering from spasticity of cerebral origin as well. Therefore, ITB pumps have been implanted to treat spastic hypertonia in patients with conditions such as stroke [39, 59, 60, 74], cerebral palsy [61, 32, 37], multiple sclerosis [79], or traumatic brain injury [4, 12]. Importantly, the U.S. Food and Drug Administration (FDA) has offered approval labeling to ITB for managing severe spasticity of both spinal (in 1992), and cerebral origin (in 1996) [54, 75].

Taking into account the multifaceted clinical profile of spasticity, it becomes apparent that ITB therapy, despite its overall favorable impact in muscle hypertonia and functional performance of the patient, should be individualized in order to meet the particular requirements of both the underlying pathology and the affected population. Such characteristic paradigms of patients needing particular pre- and post-ITB management are the pediatric population and the MS patients. In children and adolescents suffering from cerebral palsy, for instance, despite the reported benefits from chronic ITB infusion, critical issues regarding selection criteria and rehabilitation management remain to be answered [1, 6, 32, 64]. Similarly, sufferers from MS constitute a particular cohort of patients due to the unpredictable and progressive nature of their disease. These patients may prove to be more sensitive to ITB therapy compared to patients with other diagnoses, and may need lower doses of the medication both for inducing a positive result in baclofen screening trial and maintaining the post-implantation neurological benefits [25]. Moreover, implantation of ITB pumps is strongly advised to be offered to patients with MS at earlier stages of the disease, before a significant amount of ambulatory ability is lost. This kind of treatment, however, may prove particularly beneficial even at late stages of the disease i.e. when sufferers are commonly wheelchair bound; more comfort and easier caregiving can substantially improve the quality of life of those debilitated individuals [27].

The outcomes following ITB therapy can vary considerably, depending on the underlying disease, the preoperative functional state of the sufferer, the experience of the attending neuromodulation team, and the commitment of the patient to the long-term follow-up sessions. Furthermore, the postoperative dose-titration of infused baclofen is of great importance. The whole process aims to achieve maximum clinical improvement with minimum systemic unwanted manifestations; occasionally, this may prove to be a highly-demanding task and may require a long follow-up period until the desired effect is accomplished.

It is generally acknowledged that the reduction in muscle tone, irrespectively to the underlying disease (i.e. spinal cord injury, MS or cerebral palsy diplegia), is more pronounced in the lower limbs than in the upper limbs or trunk [23, 34, 58, 68]. ITB therapy offers a substantial decrease in the Ashworth scale score and average spasm score in patients suffering from chronic stroke [2, 60] or acquired brain injury [57]. However, spasticity of cerebral origin needs approximately three times higher doses of ITB in order to be reduced compared to the doses in spasticity of spinal origin. Overall, ITB therapy has been documented as a highly-effective treatment of otherwise refractory spasticity of either spinal or

cerebral origin. Reductions in muscle tone, spasm frequency and spasticity-related pain, and improvements in ability of ambulation, wheelchair seating, sleep, speech and swallowing, as well as ease in patient care giving have all been reported as positive sequelae following ITB therapy [8, 17, 33, 84].

Emerging applications

Movement disorders

Over the last two decades, ITB has been established as an effective therapeutic method for otherwise refractory spasticity. The accumulated promising data from reported series of patients receiving ITB therapy together with the fact that spastic hypertonia commonly coexists with other neurological disorders have constituted a solid basis for offering this kind of treatment to patients suffering from other movement disorders. *Dystonia* is a severe, incapacitating neurological disorder that is characterized by sustained muscle contractions that cause twisting, repetitive movements, and abnormal postures [28]. Recently, baclofen pumps were implanted in patients suffering from generalized primary or secondary dystonia with satisfactory outcome [3, 26, 94]. Dystonia scores were significantly decreased compared to baselines values and improvements were reported in cases of medically-refractory secondary dystonia, in whom cerebral palsy or traumatic brain injury coexist [3]. However, the exact mechanism of action, the selection criteria of suitable candidates, as well as the optimal placement of the catheter tip within the spinal canal remain to be determined. Interestingly, the range of indications of ITB therapy is steadily increasing with great benefit in the quality of life of sufferers from other less common neurological disorders, albeit, such as amyotrophic lateral sclerosis [51, 52], status dystonicus and Hallervorden-Spatz disease [44], Freidreich's ataxia [83] and stiff-man person [80, 91]. The post-ITB functional outcome of these patients remains unpredictable; the promising results of these studies, however, will certainly encourage further research in this field in order to define the potential role of this neuromodulatory method in these incapacitating disorders.

Vegetative state

Vegetative state may develop following severe brain injury due to trauma, anoxia or other pathology; its management has proved to be particularly difficult, if not unattainable. Notably, a considerable percentage of these patients (25–30%) [9, 13, 24] develop dysautonomic abnormalities during the initial recovery stage, which last an average of 74 days [9]. This dysautonomia syndrome, known also as sympathetic storm [15], involves paroxysmal episodes, which may last longer than 1 week and are characterized by hypersudation, tachycardia, arterial hypertension, muscle hypertonia, hyperthermia, and increased respiratory rate [9]. Diffuse axonal injury, cerebral hypoxemia, brainstem lesion, and bilateral diencephalic lesions have been correlated with autonomic dysfunction [24]. This condition is usually refractory to antiadrenergic and analgesic drugs and results to prolongation of artificial ventilation of the patient and considerable delays in his/her rehabilitation program. ITB was first associated with improvements in autonomic instability in 1997, when it was continuously administered in patients with supraspinal spasticity [12]. Becker *et al.* [13] first reported on six patients (four of them were in a vegetative state) suffering from pronounced autonomic dysfunction and severe tetraspasticity from either hypoxic or traumatic brain injury; following a positive response to a screening baclofen trial, a pump for chronic ITB therapy was implanted to all of them. Patients experienced dramatic reduction in most of their dysautonomic symptoms and thereafter, no additional medication was necessary. In 2000, the same group reported on four patients suffering from dysautonomia syndrome and severe midbrain syndrome (one of them was in a vegetative state) [14]. All but one of them responded successfully to intrathecal or intraventricular infusion of 250–400 μg baclofen per day and their autonomic instability disappeared. More importantly, two of the patients presented great improvement in their conscious state and ITB therapy was discontinued. The third patient, being in a persistent vegetative state, required continuous medication. Two years later, Cuny *et al.* offered continuous ITB therapy in four patients suffering from severe head injury and paroxysmal dysautonomia [24]. All of them presented dramatic improvement in their recovery, while their autonomic instability subsided. However, authors pointed out that ''there was no scientific background to think that baclofen could improve recovery independently of dysautonomia''.

It is known, that, in 1996, FDA approved the use of ITB for treating spasticity from traumatic brain injury providing that one year has elapsed from impact. In 2003, Turner reported on six pediatric patients suffering from spasticity, dystonia, and autonomic storming following severe head injury, who were intractable to all conventional medications [89]. A baclofen pump was

implanted to all of them and offered great improvement. The patients could be weaned from all oral and intravenous medication for hypertonia and autonomic dysfunction, and most of them became much more alert and interactive. Finally, Taira and Hori reported on a severely tetraspastic patient being in a persistent vegetative state who, unexpectedly, recovered dramatically following continuous ITB infusion [85].

At present, although the pathophysiological background of ITB treatment in spinal spasticity is well established, the mechanisms of action of baclofen in supraspinal spasticity remain unknown. GABA-b receptors are widely distributed throughout the CNS and have been implicated in tonic inhibitory control of blood pressure and sympathetic activity in animals [5, 18, 87]. The exact location of GABA b receptors, however, which are involved in supraspinal spasticity and autonomic dysfunction treated by ITB has not yet been fully understood [14]. Currently, there is no pathophysiological hypothesis which could explain the role of ITB in alleviating dysautonomic symptoms and improving recovery in patients with severe brain injury. Further investigation in the acute medical setting and research on pharmacological dynamics of baclofen within CNS are needed in order to clarify the potential role of ITB therapy in the recovery of these severely ill subjects.

Pain syndromes

The antinociceptive effect of baclofen has been known from animal experiments since late 1970s [95]; however, it has been used only sporadically for the management of *central pain* in patients *with coexisting spasticity* after stroke or spinal cord injury. In 1992, Herman *et al.*, in a double-blind, randomized study, investigated the effect of ITB (50 μg) in patients with neuropathic and spasm-related pain secondary to spinal cord injury, MS or transverse myelitis [38]; a significant reduction in both types of pain was documented, although musculoskeletal (low back pain) remained unaltered. Few years later, Taira *et al.* reported on 14 patients suffering from central pain secondary to stroke or spinal cord injury who received intrathecally 50–100 μg baclofen [86]. Nine of them experienced significant reduction in pain severity and improvement in coexisting allodynia and hyperalgesia. In 1996, Loubser and Akman observed, following ITB therapy, reduced musculoskeletal pain in 10 out of 12 patients who suffered from severe spinal cord injury and mixed pain syndromes. However, no considerable decrease in neuropathic pain was noticed in these patients [50]. Recently, ITB was shown to produce complete relief of painful lower limb paresthesias for a period of 20 months in a patient suffering from MS [31].

The role of baclofen in alleviating painful conditions associated with autonomic dysfunction has also been investigated although in limited series of patients. Van Hilten *et al.* evaluated the efficacy of ITB therapy in seven women suffering from reflex sympathetic dystrophy with multifocal or generalized tonic dystonia [90]. Three patients regained normal hand function and two of them, were able to walk again. In another patient who received ITB chronically, the pain and violent jerks disappeared. In 2002, Zuniga *et al.* observed decreased allodynia and pain, as well as marked improvement in autonomic dysfunction following ITB infusion in a woman with intractable, long-standing complex regional pain syndrome, type I [99]. Several studies have reported a beneficial effect of ITB in patients with somatic pain, such as low back pain and radiculopathy. Vatine *et al.* described significant pain reduction for up to 6 hours following a single injection of 250 μg baclofen in patients with low back pain due to root compression syndrome [92]. Similar favorable response was reported by Zuniga *et al.*, when ITB therapy was offered in five patients with chronic low-back pain and lumbosacral radiculopathy [98].

Over the last decade, the combination of baclofen with other intraspinal analgesic agents such as morphine and clonidine has evolved to be a challenging new field for research and clinical practice. In 1992, Middleton *et al.* reported on a 32-year-old woman with an established incomplete tetraplegia suffering from intractable painful anal spasms [62]; a baclofen pump had been implanted with moderate improvements in her symptoms. Substantial decrease in muscle spasms frequency and pain severity was documented when clonidine was added to baclofen in the pump reservoir. The combination of intrathecal baclofen with morphine provided long-term pain relief (>20 months) in another patient with central deafferentation pain and spasticity [31]. The analgesic effect was also enhanced when baclofen and morphine were co-administered intrathecally in a patient with failed-back syndrome [98].

Various mechanisms have been suggested or postulated in order to explain the analgesic effect of baclofen; these, however, have not yet been clarified. These mechanisms include antagonism to substance P [76], presynaptic inhibition of primary afferents or inhibition of neurotransmitter release from primary afferents [29], noradrenergic involvement [78] or cholinergic activation [41]. Perhaps, the key element in the enhanced analgesic

effects when baclofen is infused in combination with morphine or clonidine result from activity at multiple sites because the active sites of baclofen in the CNS differ from those of other drugs [47]. It is an important parameter that such drugs have proved to be compatible when are co-administered intrathecally for at least 30 days [81, 88]. Taking together all the above issues, it becomes obvious that neuromodulation practitioners face a great challenge for further investigation and clinical studies ahead. Undeniably, the role of intrathecal baclofen as an analgesic agent needs to be established through extended controlled, randomized and placebo-controlled studies. At present time, it seems that ITB may be offered in patients who have already been implanted a device for intrathecal analgesia and who experience either inadequate pain relief or untoward effects from opioids, local anesthetics or clonidine [82].

Spinal cord stimulation and ITB

Finally, another interesting line of research which has provided promising results, is the combination of spinal cord stimulation (SCS) with ITB therapy in patients suffering from otherwise intractable neuropathic pain [48, 49]. Linderoth *et al.* studied the combination of the above two neuromodulatory interventions in 43 patients suffering from neuropathic pain of peripheral origin responding poorly to SCS [48]. The authors concluded that, in carefully selected patients, ITB enhance the analgesic effect of SCS; moreover, it can be offered as single therapy in selective cases in which SCS is contraindicated or fails to improve pain.

Future directions

The field of ITB therapy offers unlimited opportunities for research and clinical studies. A series of key issues that may play an important role in the development of this area are presented in the following sections. First of all, the selection of suitable candidates for ITB therapy is of paramount importance. Screening bolus baclofen has proved indicative in the majority of cases; however, this trial should never be conducted in a simplistic way. It has been shown that in cases of diffuse hypertonia secondary to traumatic or anoxic brain injuries, the post-trial effect is not as profound as in spinal cord lesions [12]. Generally, patients who have limited residual motor and cognitive function respond poorly to ITB bolus test. Hence, doses up to 300 μg are justified before concluding that ITB is ineffective; moreover, positive reactions to the drug may delay for more than 4 hours [73]. These parameters should be always taken into account before drawing conclusions on patient's suitability for ITB therapy. Experienced neuromodulatory teams and research groups worldwide, in close collaboration with the newly-formed Neuromodulation Committee of the World Federation of Neurosurgical Societies (WFNS) and other relevant committees and scientific societies should create an ethical and scientifically solid framework of guidelines which will enhance the role of ITB in current neuromodulation practice and its wider successful use in the clinical setting.

During the pre- and post-implantation periods, various assessment tools are used in order to measure the neurological deficit of the patient or evaluate the functional outcome of the procedure. Over the last two decades, Ashworth scale [7], modified Ashworth scale [16], Penn Spasm Frequency Scale [69], and Tardieu scale [63] have been proved to be valuable standard measures for assessing patients before and after ITB therapy. However, these scales have considerable limitations. For instance, they are largely dependent on examiner's experience and interpretation of findings and it is difficult to be reproduced objectively by other members of the neuromodulation group. Moreover, Ashworth scale fails to assess velocity-dependent abnormalities that characterize spastic hypertonia, while Tardieu scale does not record the dynamic component of the movement which is elicited in rest. On the other hand, post-implantation outcome measures evaluate selected impairments rather than the overall functional improvement of the patient. It is of great importance to design new assessment tools such as the Canadian Occupational Performance Measure (COPM) that will reflect better the patient's and family's satisfaction from ITB therapy rather than to focus on individualized neurological findings [22, 46]. The current line of research tends to develop high-technology motion-analysis software that will enable examiners to evaluate objectively the range of motion in each affected segment of the body and analyze multi-component movements, which are otherwise difficult to be assessed, such as gait and standing ability. However, such systems as well as sophisticated electrophysiological and biomechanical instruments are quite expensive, require experienced operators and are available mainly in academic centers rather than in everyday clinical setting.

From a surgical point of view, the placement of the tip of the catheter within the spinal canal has been strongly argued. Threading the tip of the catheter up to the level of the sixth-seventh thoracic vertebra (T6–T7) has been shown to be effective in reducing muscle tone in both

upper and lower extremities in patients suffering from quadriparetic cerebral palsy [34], tetraplegia secondary to spinal cord injury [20], post-stroke hemiplegia [60], and acquired brain injury [58]. Further randomized prospective comparative trials are needed in order to assess the safety and clinical efficacy of the higher placement of the catheter in comparison with its conventional placement in the thoracolumbar region. Towards this aim, measurements of drug concentration in the cervical region following different placements may also help to determine whether placement in the cervical area results in higher concentrations of baclofen compared to placement to lower thoracic areas [26].

Successful management of patients who receive ITB therapy requires a committed, experienced, multidisciplinary team which will ensure the smooth transition between the different stages of the therapy, during both pre- and post-implantation periods. Physical and occupational therapists, neurologists, neurosurgeons, othopaedic surgeons, pain practitioners, physiotherapists, and neuropsychologists, supported by well-educated nurses and technical staff will select the best candidates for ITB therapy, offer surgical implantation of the pump in a safe way, and enforce patients and caregivers physically and psychologically to achieve the maximum functional benefit from this type of therapy.

Timing of initiating ITB is also of paramount importance, particularly in those candidates who should be offered other types of corrective or reconstructive orthopaedic surgery such as tenontometatheses, tendon lengthening, or urological surgery for treating neuropathic bladder [10, 32, 70]. Before deciding the implantation of a pump, it is mandatory to evaluate the possible role of spasticity in functional capacity of the patient. Many sufferers take advantage from their hypertonia in order to stand, seat in wheelchair or walk. In such cases, the loss of these abilities may outweigh the gain from the implantation of an ITB pump.

Current neuromodulation practice is steadily tending towards less ablative, minimally-invasive procedures that offer safety, reversibility, and accuracy. From a technical perspective, ITB therapy is closely bound to the subcutaneously implanted pump which is driven telemetrically by a battery-operated system. Current pumps are too big, cumbersome and quite expensive, presuppose high expertise in programming of the ITB delivery, need refilling every 3 months and replacement every 5–7 years and more importantly, ''bind'' indefinitely the patient with the attending neuromodulation team. It is expected that biotechnology will produce more sophisticated pumps, smaller in size, operated by rechargeable batteries, with bigger reservoirs and easier programming of their function.

Conclusion

Neuromodulation has been one of the most rapidly evolving fields of current neurosurgical practice. Closely bound with basic neurosciences such as neuroanatomy, neurophysiology, and neurobiology and supported by high-resolution digitalized neuroimaging studies and sophisticated biotechnology advances, neuromodulation offers unlimited opportunities for experimental and clinical studies. In the foreseeable future, intrathecal baclofen therapy, an established neuromodulatory intervention for certain neurological disorders, will be undeniably at the first line of research. In the years to come, the neurochemical and neurophysiological mechanisms of action and the unknown interrelationships of baclofen with neural networks are likely to be elucidated; following such a progress, ITB therapy may become an effective therapeutic method, not only for spasticity, but for many other incapacitating and disabling diseases of the central nervous system.

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Intrathecal baclofen therapy: indications, pharmacology, surgical implant, and efficacy

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Summary

Intrathecal baclofen (ITB) therapy is an option for those in whom predominantly lower extremity spasticity is severe, problematic, and intractable to oral doses of medications and/or focal treatment. When delivered to the lumbar area, ITB avoids high concentrations from reaching the brain (4:1 ratio lumbar to brain cisterns).

A screening test dose is done prior to implanting the pump via a lumbar puncture with 50 μg baclofen, working up to 100 μg if necessary.

There are two [2] types of pumps. The electronic programmable type has the advantage of flexibility of dosing and frequent change of doses for fine-tuning the patient's optimal dose. The mechanical constant flow type has the advantages of 1) being gas driven and not needing battery replacement, and 2) not needing a programmer to refill, thus allowing geographically removed patients to benefit from ITB.

Catheter complications are reduced by using a shallow-angle paramedian oblique insertion to the spine, and meticulous anchoring of the catheter. Threading the catheter to T6/7 rather than the traditional T10/11 can allow upper limb relief also.

Long term efficacy is excellent, although catheter complications are frequent, and if not recognized and treated, can lead to significant effects of withdrawal of baclofen.

Keywords: Neuromodulation; baclofen; intrathecal pump; spasticity; surgical implant; ITB.

Definition of spasticity

Spasticity is a velocity dependent increase in muscular tone and stretch reflexes [17]. It is a part of the upper motor neuron syndrome caused by a lesion to the central nervous system. Thus spasticity can be seen in a variety of neurological disorders, inclusive of spinal cord injury (SCI), multiple sclerosis (MS), stroke, acquired brain injury, cerebral palsy, and others.

Spasticity therapy

Decisions to treat spasticity are made after comparing the problematic effects of spasticity with the potential side effects and benefits of therapy. Main problematic effects of spasticity are individualized but often include pain, difficulty with ambulation or transfers and activities of daily living, interrupted sleep, difficulty with hygiene in specific areas (e.g. palm or groin), seating difficulties, and contractures. However, many people with spasticity may not find the spasticity problematic, in which case it can be left untreated. Some are indeed aided by spasticity. For example, many people with significant quadriceps spasticity find they are able to use their spasticity to perform standing transfers or ambulate short distances, or they use that spasticity to help "swing" their legs into bed.

If spasticity therapy is needed, a stretching routine should be initiated. There are various medications available for spasticity, including oral baclofen, tizanidine, clonidine, diazepam and other benzodiazepams, and dantrolene. In addition, some medications have been reported as being useful in some cases such as anti-epileptics (gabapentin) and cannabinoids (commercially available orally as Cesamet, Marinol, and, in Canada, Sativex for sublingual use). Focal problematic spasticity can be treated using botulinum toxin. Although it is a focal therapy, patients with generalized spasticity can often obtain benefit from it if a focal area of spasticity is deemed most problematic (e.g. the hip adductor spasticity in multiple sclerosis causing hygiene and dressing problems). A full review of these oral, sublingual, and focal therapies is beyond the scope of this chapter.

Intrathecal baclofen (ITB) therapy has been an increasingly available option for those in whom predominantly lower extremity spasticity is severe, problematic, and intractable to oral doses of medications and/or focal treatment.

Pharmacology of intrathecal baclofen

ITB therapy is the use of liquid baclofen delivered from a pump placed in the lower abdominal wall, connected to a catheter tunnelled through the subcutaneous space, around to the spine, then directly into the intrathecal space around the spinal cord. This focuses the medication at the tissues most responsible for spasticity, with little exposure of the brain to the medication, thus allowing for excellent lower body spasticity control without the significant sedating side effects of oral medications.

Baclofen is a structural analog of gamma-aminobutyric acid (GABA). It binds to the $GABA_B$ receptors in lamina II and III, thus blocking mono and polysynaptic reflexes [4]. Due to the hydrophilic nature of the drug, baclofen taken orally results in little absorption into the cerebrospinal fluid (CSF). Thus, large doses orally are required, resulting in significant side effects (e.g. sedation) as the concentration that reaches the brain approximates that reaching the spinal cord. Penn and Kroin compared the use of oral baclofen 60 mg/day to intrathecal 200 μg/day and found the CSF concentration with the intrathecal delivery was about 16-fold that of the oral delivery route [26]. The key to success with intrathecal therapy is that despite high concentrations of baclofen in the CSF of the lumbar area, only ¼ of that concentration is detected in the cisterns of the brain [15, 16].

The onset of action of continuous-infusion baclofen (assuming the line is primed) is within 6–8 hrs, with maximum activity by 24–48 hrs [25]. However, bolus delivery of intrathecal baclofen can relieve spasticity within 30 minutes to one hour. The CSF levels after bolus diminish rapidly in the first 1–2 hrs (elimination half-life 1.5 hrs) [15], but the time to get absorbed into lumbar grey matter and have peak onset of action is 3–4 hrs.

Intrathecal baclofen is preservative and antioxidant free. As many preservatives and antioxidants (e.g. alcohol, phenol, and formaldehyde) are toxic to the central nervous system, one also must use preservative-free saline when diluting the baclofen for use with constant infusion mechanical pumps.

Indications and patient selection for intrathecal baclofen therapy

Inclusion criteria for ITB therapy include spasticity due to stroke, spinal cord injury, multiple sclerosis, brain injury, and cerebral palsy. In traumatic cases, inclusion criteria include only those at least one year post injury. ITB is only indicated if the patient and caregivers have realistic and obtainable goals to achieve by treating the spasticity (e.g. improving mobility, pain, or hygiene). The patient and family must be committed to and be relied upon for the long-term follow-up care required.

As the catheter is usually introduced in the lumbar spine and threaded up to approximately to the T10 vertebral body (i.e. lumbar spinal cord level), ITB is most beneficial in treating lower body spasticity such as for spinal cord injury [24], multiple sclerosis (MS) [2], and cerebral palsy diplegia. In those with both problematic upper and lower extremity spasticity, the patient, family, and clinician need to be aware that the upper extremity spasticity will not be as greatly affected with this approach. In these cases, one can use either concomitant focal treatment to the upper extremities with botulinum toxin, continued use of concomitant oral therapy, or, as being done more and more frequently, thread the ITB treatment catheter up to the mid thoracic area (T6-7), thus affecting both upper and lower extremity tone. This technique has been used with success in those with spasticity from quadriparetic cerebral palsy (adults [21] and children [10]), tetraplegia from spinal cord injury [1], post-stroke hemiplegia [9, 20, 28], and acquired brain injury [19]. For these groups for whom spasticity is of cerebral origin, Meythaler *et al.* suggests that spasticity should be present for at least 6 months, be at least grade 3 on the Ashworth scale (equivalent of 2 on the modified Ashworth scale), and affect at least 2 limbs to this degree [21]. The pharmacokinetic effects of infusing baclofen at the T6-7 level have not been studied to the same degree as lower infusion; hence, the ratio of baclofen at this infusion site compared to the cisterns of the brain is unknown (the lumbar to brain cisterns concentration ratio is 4:1). As the infusion is more rostral in these cases than in cases of infusing at T10-11, one may suspect the side effects, from higher concentrations reaching the cerebrum, may be greater. There have not been randomized prospective comparative trials to assess whether the higher placement has less beneficial effects on the lower limb spasticity compared to lower placement. Presumably, based on the fact that the baclofen is mostly absorbed by the cord at the level it is infused, one would suspect that tip placement at the T6-7 level would benefit lower limbs less than placement at the traditional T10-11 level.

Caution must be used in selecting intrathecal baclofen therapy in those who require spasticity to stand or ambulate, and attempts should be made before implantation to determine the extent of benefit of reducing spasticity versus the consequences of eliminating it. Likewise is the case for those who have compro-

mised truncal tone, and further reduction of truncal tone would cause significant problems with seating, etc. Hypersensitivity to baclofen is a contraindication to ITB therapy.

Intrathecal baclofen trial

Once the decision is made that intrathecal baclofen is appropriate for a particular patient, the patient undergoes a trial of intrathecal baclofen. Note that this trial is NOT done unless there is an understanding that he/she will go on to get a pump implant if the trial is successful. Thus if costs, the logistics of getting refills, etc make the eventuality of placing a pump impossible, there is no point in undergoing a trial. The main purpose of the trial is to be sure that intrathecal baclofen will ablate the problematic spasticity, or lessen it, and that underlying contractures are not the main problem. The trial should also not be used to assess if the person will maintain function such as ambulation or transfers with intrathecal baclofen therapy, as the test dose may make the lower limbs extremely flaccid, making transfers difficult and taking away the ambulatory ability. The patient needs to understand that the pump dosage can be fine-tuned to a much greater degree than the trial dosage to allow for the patient to maintain some tone for ambulating and other activities.

The test dose of baclofen in an adult is generally 50 μg in 1 ml given via lumbar puncture or spinal catheter bolus injection. This can be done in the outpatient setting if the appropriate personnel and equipment are available in case of emergency. Blood pressure cuff, oxygen monitor, pulse monitor, and intravenous set-up should be ready for use if needed.

The person is examined pre-test dose to ascertain Ashworth scores of the lower limbs, and these are documented. Patient perception scores such as the Spasm Frequency Scale, and the Visual Analogue Scale for those in whom spasms are painful should be documented. The person is then re-examined ½ hour post injection, then again at 1, 2, 4, and 6 hrs post injection. In addition to measures of spasticity, vital signs of blood pressure and heart rate need monitoring. The patient may get up between assessments, in fact is encouraged to, to be able to assess the effect of the test dose on decreased triggered spasms during transfers, mobility, etc.

A positive response to an ITB test dose is defined as a 2-point drop in the average Ashworth score of the affected limbs, or 2 points on the spasm frequency scale. Some authors use a drop of a mean of 1 on the Modified Ashworth Scale (MAS) in cerebral origin spasticity as being positive [9]. Considering the test dose is being placed caudally at L2-3 or L3-4, and that many with cerebral origin spasticity may have upper extremity spasticity with the plan of placing the catheter at mid-thoracic level where it would have more effect on the upper limbs, perhaps this more modest goal of achieving a drop of 1 on the MAS rather than 2 is more realistic.

If insufficient effect is noted with the 50 μg test dose, another test dose can be done on another day (as early as the following day) of 75 μg in 1.5 ml, and then 100 μg in 2 ml on a further day if needed. If response is not adequate with 100 μg test, the person is not appropriate for ITB therapy. An option for the test dose is to insert a spinal catheter for the initial test dose and leave in place for the following days if needed for a larger dose. The alternative is to give the test dose via single lumbar puncture injection, and if larger dose is later needed, the injection is repeated with larger dose. In our experience, we use the latter method as we have not had to go to higher doses than the initial 50 μg bolus other than in one case in which we went up to 75 μg test bolus with good response.

The Medtronic SynchroMed II product monograph suggests weaning the oral medications prior to the test dose [18], but this can be extremely difficult for most of this patient population, and there has been no need to do so in our experience. Once the pump is implanted the oral medications can be weaned as the pump dose is increased.

Choosing the type of intrathecal pump

Once the decision is made to implant an ITB pump, the type of pump needs to be chosen. There are clinically available 2 types of propellant technologies for these pumps: electrical programmable pumps and mechanical constant flow pumps. The electrical programmable one is battery operated (SynchroMed II, by Medtronic Inc, Minneapolis, Minnesota) and thus needs to be replaced every 5–7 years. The major advantage with the programmable pump is the flexibility of programming various rates of medication dosing throughout the day, and the ability to frequently change dosing by reprogramming the rate. However, the pump needs to be refilled by a person with expertise and access to a programmer, thus necessitating access to a large centre that has an ITB pump program. Figure 1 depicts the SynchroMed II pump and handheld programmer.

Fig. 1. The SynchroMed II pump and handheld telemetry programmer. Photo provided courtesy of Medtronic Inc

The mechanical constant infusion pump is gas driven. It has 2 chambers, one filled with compressible gas (fluorocarbon), the other being the medication chamber (Fig. 2). When the medication chamber expands during a refill, the fluorocarbon gas in the gas chamber compresses. The compressed gas then expands, thereby driving medication from the drug chamber into the catheter.

The mechanical pump has a pre-set flow rate (between 0.5–2.0 ml/day), thus the daily dosage is adjusted by changing the dilution of the medication in the pump. This pump therefore, does not have the flexibility of frequent dose changes as the dose can only be changed when the pump is refilled and the dilution changed. However, the major advantages are that it is not battery driven, thus does not need replacement, is much less costly, ($5900.00 Canadian for the Codman 3000 pump, $9550.00 Canadian funds for the SynchroMed II: quotes as of September, 2005), and it is refilled without a programmer. There are presently 2 constant infusion pumps available on the market, Medtronic's IsoMed Constant Flow Infusion System (Minneapolis, Minnesota), and the Codman's Model 3000 Constant Flow Implantable Pump with Bolus Safety Valve (Raynham, Massachusetts). The latter pump was previously known as Arrow 3000 and, before that, Therex 3000. Previously available was the Infusaid by Pfizer. The life span of these mechanical pumps does not depend on batteries, thus do not require to be changed. We follow a patient with an Infusaid pump that is over 14 years old, and patients with Therex 3000 pumps (now Codman 3000 pumps) that are up to 11 years old. As these pumps do not require programmers, we have trained nurses to refill these pumps, thus allowing people who are severely disabled and difficult to transfer to our centre, or live a significant distance from our centre, to benefit from intrathecal therapy. The pump may be refilled at a centre remote from ours, and the information transmitted to us by facsimile. These pumps are very accurate (flow rates within 94% of predicted) and reliable (no pump failures have been reported) [6].

Another advantage of the constant infusion pumps includes the raised septum in the middle, which is easily palpated through the skin, making the refill septum easily accessible (Fig. 2). This is present on both models of the constant infusion pumps (i.e. IsoMed and Codman 3000). In the Codman 3000 the bypass port is easily accessible within the same septum as the refill septum, but with the special bolus needle (Fig. 2, left side). The

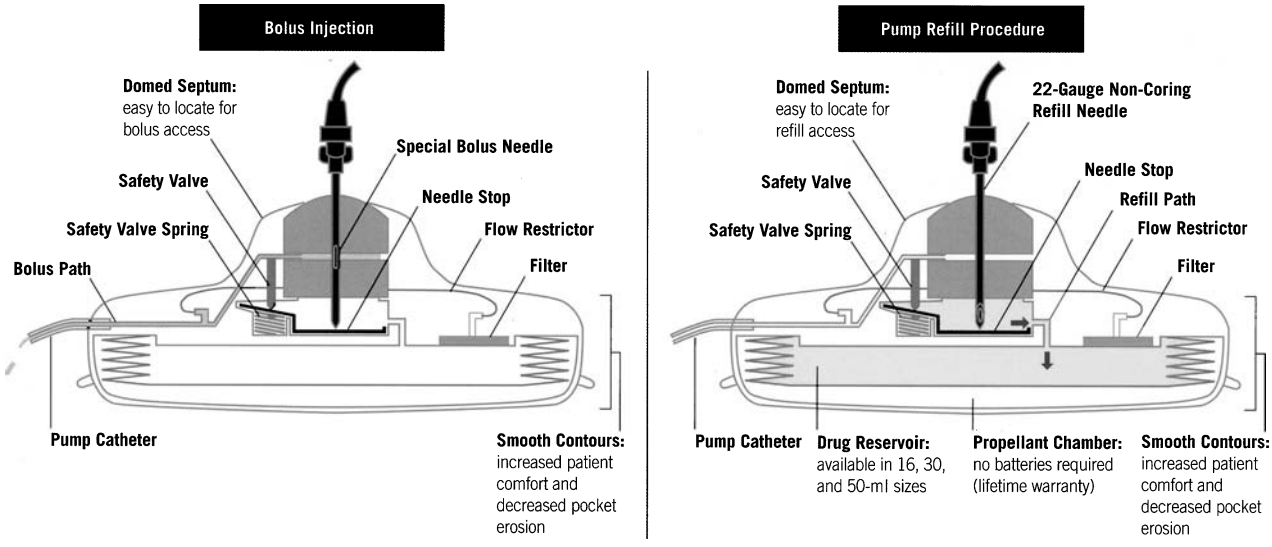

Fig. 2. The Codman 3000 Constant Flow Implantable Pump. On the left is the procedure for accessing the bypass port, on the right is the refill procedure. Photo provided courtesy of Codman Inc

IsoMed has a separate bypass port, which can only be accessed by a 25-gauge needle, making accessing the bolus path for diagnostic and therapeutic procedures difficult at times.

Considering the pros and cons of each type of pump, our team recommends the programmable SynchroMed II in a person who needs fine tuning of dosage, especially in an ambulatory person where frequent dose changes may be a necessity to prevent taking away too much tone and thus decreasing ability to walk and stand. However, this person must have easy access to a centre with a programmer.

We recommend a constant flow mechanical pump (usually the Codman 3000, as the bypass port is more user friendly) in those for whom cost is a consideration, those who are geographically remote from our centre, those for whom transport is an issue (e.g. in personal care homes), those who do not stand or ambulate and thus fine tuning is not an issue, and those who have had a previous programmable pump at a very stable dose but need replacement due to battery failure.

ITB pump implantation

With implantation, one must consider the following: the pump site, the level and technique of entering the spine, and how far proximally to place the tip of the intrathecal catheter. The decision regarding pump site location should be based on consultation preoperatively with the patient and the team that will be doing the long-term refills. It should be placed in a location free of orthosis, wheelchair and restrictive clothing. If a body brace needs to be worn, the orthotist needs to be consulted regarding placement of a foramen to accommodate the pump. The pump should not be placed on the belt line, near the pelvic bone or rib cage, on near ostomies, feeding tubes etc. If a scoliosis is present, the implant should be on the convex side of the curve where possible. As the curve progresses, if the pump is on the concave side, it can get progressively more difficult to locate and fill. The pump site should be marked in sitting. For very thin patients, and for those in whom possible skin erosion with body jackets is a concern, subfascial pump placement should be considered. This implant under the anterior rectus abdominus and external oblique fascial layer provides for better soft tissue coverage and minimize the risk of skin breakdown [14]. As the fascia is not thick, the pumps implanted as such should not be much more difficult to refill, although this is certainly a possible concern. Recently, Ross *et al.* reported a case of implanting a pump in the lower thoracic, paraspinal region to minimize the differential motion between the spine and the pump in a person with recurrent catheter migrations [29]. However, this technique was not successful until the catheter was secured to the fascia with a butterfly anchor, suggesting perhaps the more important issue in this case was catheter fixation rather than pump placement site.

Specific details of making the pump pocket will not be discussed, other than to say the incision should be either cranially or caudally to where the pump will be placed, not directly over it, as the scarring would make future location of the septum difficult.

The spinal catheter is the next consideration. Long-term complications of the catheter can be minimized with a mid-upper lumbar dural entry level, a shallow-angle paramedian oblique insertion trajectory (Fig. 3), and meticulous anchoring of the catheter. The entry of the needle through the skin or fascia should be 1–1 ½ vertebral levels caudally to the interlaminar space targeted for dural puncture, and 2 cm lateral to midline of the L2-3/L3-4 interlaminar space (Fig. 3). This technique avoids the catheter from contacting the spinous processes, which can erode the catheter over time, and allows easier rostral threading of the catheter in the intrathecal space [8].

Catheter dislodgements are frequent if no anchoring is used [7]. Thus the catheter should be anchored to the lumbo-dorsal fascia (not subcutaneous fat) with heavy, non-absorbable suture material to keep the anchor in place [7].

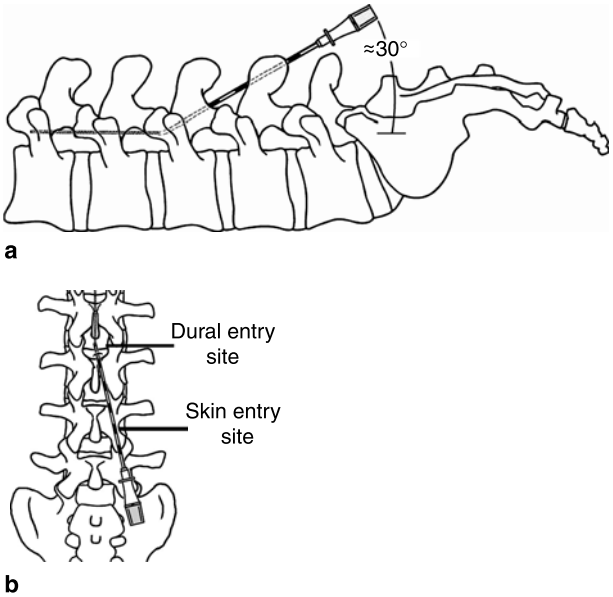

Fig. 3. The shallow angle, paramedian, oblique trajectory for the spinal insertion of the intrathecal catheter. (a) Sagittal view, (b) AP view. Photo provided courtesy of Medtronic Inc

The placement of the tip catheter within the spinal canal is determined preoperatively based on goals of targeting upper limb spasticity in addition to lower limb spasticity. If targeting upper limb spasticity is of importance, then the catheter can be threaded up to the T6-7 level, with good outcomes as referenced above. To estimate the amount of catheter needed to thread up the intrathecal space, one can measure, on the surface of the skin, the distance between T6-7 and the insertion point, L2-3 or L3-4.

Dosing post implant

The starting dose of ITB post-implant is dependent on the effectiveness of the screening trial dose. If the effect of the screening dose is less than 8 hrs, the starting dose (dose per 24 hrs) is double the screening dose, such that an effective screening dose of 50 μg lasting less than 8 hrs would indicate a starting dose of 100 μg/day. If the screening dose was effective for more than 8 hrs, then the starting dose per day would be the same as the test dose.

For programmable pumps, usually start with a 500 μg/ml concentration, which allows for dosing as low as 24 μg/day if needed. Titration can be started as early as the following day post implant, increasing as needed, as much as 10% at a time. Due to ability to titrate up with a programmable pump so quickly, oral medications may be fairly rapidly tapered.

For the mechanical, constant rate infusion pumps, start with the concentration of drug that will give an appropriate starting dose per day. For example, if using a 0.5 ml/day pump, and starting with a dose of 100 μg/day, then one starts with a concentration of 200 μg/ml (100 μg/day divided by 0.5 ml/day = 200 μg/ml). With the initial fill, start with a volume of 10 ml so that a refill can be done to modify the dose early post implant. Calculate the total dose to be placed into the pump first, i.e. Desired concentration X desired total volume (200 μg/ml × 10 ml = 2000 μg). Thus if using baclofen 500 μg/ml, use 4 ml of the baclofen (2000 μg divided by 500 μg/ml = 4 ml), then dilute with 6 ml of preservative free saline (for total of 10 ml). In a pump delivering 0.5 ml/day, this will deliver 100 μg/day to the intrathecal space. Titration of dose upward is much slower with these pumps, as the dose changes can only be made with refills.

Efficacy of intrathecal baclofen long term

The effectiveness of baclofen intrathecally is excellent. An early multi-centre study done to assess long term safety and efficacy in patients with ITB followed people with MS or SCI for 5–41 months post surgery (mean 19 months) [2]. This group found that at last follow up exam, the mean lower extremity Ashworth was 1.7, down from a preoperative mean of 3.9. Muscle spasm score dropped from 3.1 to 1.0. The therapeutic dose rose from 187 μg/day to 405 μg/day over time, although the spasm frequency score did decrease during this time, suggesting it may just take several months to really find the ''therapeutic dose''. More recently Ordia *et al.* reported similar results on long-term follow-up of people with ITB, again for spasticity of spinal origin [23]. The average length of time since implant ranged from 2 to 137 months (mean 73 months). The mean Ashworth scale had dropped from 4.2 pre-implant to 1.3 at last follow up, and the mean spasm frequency score had decreased from 3.4 to 0.6. Many of the other studies of efficacy are not as long term as the two described, thus will not be reviewed here.

Although there is excellent long-term effect of ITB, there are significant complication rates. Complication cause is often difficult to diagnose, and usually leads to acute underdosing, causing withdrawal associated with significant morbidity and mortality. The following issues must be considered with regards to long-term efficacy: the risk of loss of effect from drug tolerance, the risk of loss of effect and withdrawal from complications, and the risk of overdose. The complications causing loss of effect and withdrawal can be device-related due to catheter or pump malfunction, human error in dosing, programming or compliance, or battery-life related. Overdose is rare, and is usually caused by human error.

Drug tolerance

Drug tolerance has been reported by various authors and can range 3–20% [3]. Some authors recommend a ''drug holiday'' in which the baclofen is replaced by a medication such as morphine in the pump for up to a few weeks. A recent case report nicely describes tolerance in a patient 9 years after starting ITB therapy, with excellent effects of a 15-day drug holiday from baclofen using intrathecal morphine [30]. Coffey *et al.* stated that in their study, 6/75 developed suspected ''drug tolerance'', which was treated with a ''drug holiday'' for 3–37 days [2]. There is a comment that some started back on lower doses, some on higher doses of ITB, but no comment on whether these drug holidays were successful in resuming therapeutic effect once ITB was resumed. Similar to this study, in the literature, the effectiveness of these holi-

days is not well described, and the risks and discomfort of baclofen withdrawal during this holiday may not be worthwhile. It is likely that many cases of so-called ''intolerance'' are actually due to lack of effect due to catheter malfunction, as these catheter problems are often difficult to diagnose [5].

Device-related complications

Catheter related complications

Catheter complications are by far the most common cause of problems related to ITB therapy. In the trial by Coffey *et al.*, of 75 patients, catheter complications included 7 kinks, 8 dislodgements, 6 cuts/breaks, or about 2/3 of the device related complications [2]. Our group reported catheter problems requiring replacement in 7/17 subjects [6]. In Ordia's study following 152 people up to 137 months, there were 12 occlusions or kinks, 8 breaks in 6 patients, 2 punctures, and 2 dislodgements [23].

Pump related complications

Coffey reported that pump underinfusion occurred in 2/75 patients, and pump stall in 1/75 patients of a study of programmable SynchroMed pumps [2]. Ordia *et al.* [23] reported one ''stuck valve'' and 2 flipped pumps.

A spontaneous ''overdose'' by these pumps has not been reported. Overdose occurs by human error in calculations or programming, especially when doing concentration changes from 500 μg/ml to 2000 μg/ml, or by concomitant illnesses or medications being experienced by the patient, but not by the pump suddenly or spontaneously delivering more medication than expected.

Pump failure due to battery failure is an issue with the programmable pumps. The older pumps were expected to last 4–5 years, and the SynchroMed II for about 7 years. There is a low battery alarm, but it is difficult to hear, and Green *et al.* describe a case of death from ITB therapy withdrawal due to end of battery life and not hearing the alarm [11]. Thus once a patient is approaching the expected end of battery life for a pump, we schedule a replacement regardless of whether the alarm is going off yet.

The constant flow/mechanical pumps are not battery driven, thus do not need to be replaced. The longest running Codman 3000 pump (called Therex 3000 then) we follow was implanted in 1994, and this patient with MS is still doing well with her ITB therapy pump and the pump is still running effectively. Our group has reported on these pumps as being accurate and reliable in the long term, with accuracy of the pump delivery ranging from 90–97%, and there being no primary pump failures since first implant in 1994 [6].

Other complications

Certainly many other complications have been reported and included pump site infection, breakdown, and seroma, cerebrospinal fluid leaks, hypotonia and somnolence. Acute baclofen withdrawal from failure of the system, whether it is from a pump stall, end of battery life, catheter malfunction, or pump running dry, can be very serious. Death from withdrawal has been reported in 6 people [3]. Effects of acute withdrawal from ITB can include seizures, rhabdomyolysis, hypotension, intractable spasticity, fever as high as 43.2 degrees Celsius [12], agitation, and other organ failure. Thus prevention of withdrawal is obviously important, including education of the seriousness of withdrawal, being fastidious with refilling, programming, and scheduling (scheduling earlier rather than later, even if it means wasting significant leftover baclofen), and monitoring closely for end of battery life. Early recognition and education of recognition of acute withdrawal is of utmost importance. Early oral replacement of baclofen can be taught to patients to start as soon as withdrawal is recognized (i.e. increased spasms). Resumption of ITB therapy early is optimal. In cases where this is not possible, and oral replacement of baclofen is not adequate, intravenous diazepam has been recommended as it works quickly [27]. Dantrolene has also been reported as useful [17]. As baclofen withdrawal is clinically similar to serotonergic syndrome, the serotonergic antagonist cyproheptadine has been found to be helpful [22].

Conclusions

Intrathecal baclofen therapy is a good option in those with severe, intractable, problematic spasticity not amenable to other therapies. However, there is potential for significant complications, especially that of drug withdrawal complications from catheter dislodgment or malfunction, patient non-compliance, schedule and dosing errors, and battery failure. Withdrawal can cause significant morbidity and mortality, thus utmost care should be taken to avoid this, with proper patient selection, expertise in placing the pump and catheter, and meticulous follow-up scheduling, refilling, and reprogramming the pump. The treating interdisciplinary team needs to have an intimate knowledge of the workings of these pumps. Proper education prior to pump placement of patient and family as to what to expect from ITB therapy

in the long term can help identify real, treatable goals that can be achieved and ensure the best outcomes.

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Intrathecal baclofen in the treatment of spasticity

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Summary

Spasticity is a disorder of the sensorimotor system resulting in velocity-dependent increased muscle tone and tendon reflexes. Intrathecal baclofen is currently the most effective means of treating diffuse abnormal spasticity of both cerebral and spinal origin in the adult and pediatric patient. Careful patient assessment, selection and continued therapies are essential to a successful intrathecal baclofen management program.

Once a patient receives a baclofen pump, close monitoring is needed for dose adjustment and pump problems. Baclofen overdose and withdrawal by either system failure or human error can cause significant side effects and be life threatening. Excellent understanding of the baclofen delivery system, programming and dose effects are needed to evaluate any patient complaints.

Future uses of intrathecal pump therapy includes use of other intrathecal drugs besides baclofen (or in combination with baclofen) and the effects of placing the catheter tip at various spinal levels.

At the University of Minnesota, Sister Kenny Institute and Gillette Children's Specialty Healthcare our experience has shown excellent results with this form of therapy over the last 12–16 years.

Keywords: Neuromodulation; spasticity; intrathecal baclofen; pump; treatment; ITB.

Basic science and treatment of spasticity

Spasticity is a disorder of the sensorimotor system characterized by a velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitablity of the stretch reflex. It is one component of the upper motoneuron syndrome, along with released flexor reflexes, weakness and loss of dexterity [36].

In a cerebral injury (such as cerebral palsy, multiple sclerosis, neuro-degenerative diseases, traumatic brain injury, and stroke) the upper motor neuron syndrome occurs when there is an interruption of the descending projections from the motor neurons in the cerebral cortex and brain stem that modulate excitation of the internuncial pool of inhibitory interneurons and the alpha and gamma motor neurons. The net effect is a reduction of inhibitory influences and an increase of muscle stretch reflexes (hyperreflexia), increased muscle tone (spasticity), weakness and disinhibition of the flexor reflex (Babinski sign) [26]. Patients often demonstrate antigravity postural patterns with shoulder adduction, elbow and wrist flexion, hip adduction, knee extension and ankle plantar flexion [36].

In a spinal cord injury, afferent activity enters the cord at one level and ascends or descends without inhibition on segmental polysynaptic pathways to other levels of the cord. This results in muscle responses many limb segments removed from the afferent generators originally stimulated [36]. Spasticity with increased muscle tone, exaggerated tendon jerks, clonus, weakness and loss of dexterity occurs. Even though strong flexor muscles tend to dominate the clinical movement patterns, cumulative excitation in the cord may spill over to the flexor and extensor muscle groups [36].

Although clinicians try to lessen spasticity to improve motor control and reduce its effects on sleep, skin breakdown and pain, the presence of loss of dexterity and weakness are often more important to the decreased function of the patient [36, 35].

Treatments for spasticity include physical and occupational therapies. Oral pharmacologic agents such as dantolene sodium, baclofen, diazepam, tizanidine and clonidine are used. Local treatments include injections with anesthetics, ethyl alcohol, phenol and botulinum toxin. Surgical procedures include selective posterior rhizotomy, tendon lengthening and tendon release or transfer. For the treatment of more generalized spasticity, intrathecal antispastic drugs such as baclofen and morphine are used.

At this time, baclofen is the most commonly used intrathecal drug for spasticity management. Continuous intrathecal baclofen can eliminate spasticity when oral therapy with baclofen has failed [25]. Baclofen binds to presynaptic GABA-B receptors within the brainstem, the dorsal horn of the spinal cord, and other central nervous system sites [3, 50]. The effects of intrathecal baclofen are believed to be caused by hyperpolarization of motor horn cells [3]. Baclofen lessens flexor spasms and hyperactive stretch reflexes in hypertonus of spinal cord origin. It also benefits those with hypertonia from cerebral lesions [35]. When baclofen is delivered intrathecally, the oral side effects of drowsiness, confusion, and decreased attention are minimized [3, 33]. The administration of baclofen by intrathecal catheter delivers a greater concentration to the spinal subarachnoid space, as compared with oral delivery [37]. When the catheter is placed in the thoracolumbar and sacral regions, the lumbar to cistern drug cerebrospinal fluid concentration gradient is 4.1:1 [32]. It is thought that this concentration helps avoid the side effects of drowsiness, lethargy, and sudden respiratory arrest by minimizing the concentration of drug reaching the brainstem and cerebrum.

Adult indications and selection criteria for intrathecal baclofen

Intrathecal Baclofen (ITB) is currently the most effective means of treating diffuse abnormal spasticity of both cerebral and spinal origin [5, 38, 43]. It has FDA approval for both indications [49]. Though not FDA approved for other indications, it has been found to be helpful in movement disorders such as dystonia and rigidity [5, 19] and some pain disorders such as chronic reflex sympathetic dystrophy [54].

Patients and clinicians alike are impressed at the dramatic improvements in tone, pain, range of motion, and function after initiation ITB followed by an interdisciplinary team approach to rehabilitation [15, 38].

Patients are screened for potential efficacy of ITB by performing a test dose of baclofen via lumbar puncture before consideration of implantation. Objective measurements are perfomed throughout the day of injection to determine whether there have been changes in tone, gait quality or speed, dysphagia, dysarthria, spasm scores, pain, and other functional skills. Individual response to the test dose may be subtle or dramatic, and the clinician determines whether ITB therapy is indicated based on the result [49].

A careful assessment and selection process is essential to a successful spasticity management program which utilizes ITB therapy. Those with hemiplegia/tetraplegia will derive more benefit to the lower limb(s), although placement of the catheter tip in the high thoracic or cervical area has been found in some studies to improve tone relief to the upper extremity [23, 28]. It is generally advisable to try other methods of spasticity management before proceeding to ITB therapy, such as oral medication administration or focal injections of botulinum toxin or phenol. However, there may be certain patients in which these approaches are contraindicated or the abnormal tone is so severe that these approaches are not likely to be of benefit. Those with cognitive impairment who are sensitive to medications with sedative qualities are a good example [38] (Table 1).

Once a potential candidate is identified, contraindications to this type of therapy must be examined before proceeding with a test dose. Adverse reactions with oral baclofen such as sedation or GI upset are unlikely to occur with ITB [43]. Seizure disorders and ventriculoperitoneal shunts are not contraindications to ITB therapy as long as the primary provider for these disorders is

Table 1. *Ideal adult candidates for intrathecal baclofen therapy*

– Spastic hemiparesis secondary to stroke or other CNS insult
– Spastic paraplegia or tetraplegia due to spinal cord pathology
– Spasticity and/or dystonia due to cerebral palsy or brain injury
– Patients responsive to oral medications with unacceptable side effects or inadequate relief
– Those with inadequate response to botulinum toxin or phenol block injection therapy
– Cooperative, motivated patients with good ability to comply with clinic follow-up/therapy

Table 2. *Contraindications of intrathecal baclofen therapy*

Absolute adult contraindications for intrathecal baclofen
– Medical instability precluding spinal surgery
– Uncontrolled coagulopathy – due to risk of intraspinal hematoma
– Hives or anaphylactic reaction to oral baclofen
– Inability to access a spasticity management program or home care agency for maintenance
– Lack of response to screening trial
Relative adult contraindications for intrathecal baclofen
– History of medical non-compliance
– Pregnancy
– Arachnoiditis
– Mental illness
– Active chemical dependency
– Lack of reliable caregiver for cognitively impaired patient
– Less than 6–12 months post stroke, spinal cord injury, traumatic brain injury
– Previous failure of ITB therapy
– Upper limb tone only

agreeable to long term use of ITB. In hemiplegic patients, the unaffected limbs are not adversely affected by ITB [38] (Table 2).

Caution must be exercised in the use of ITB in those patients who are still ambulatory or actively transferring themselves. Those with abnormal tone adapt physiologically to the tone and use it to their advantage as much as possible. Patients often underestimate this factor and are unprepared for the extensive rehabilitative efforts which must ensue after placement of an ITB pump. Activities of daily living (ADL) tasks and mobility tasks must be ''relearned'' with less reliance on tone [3]. Potential candidates for ITB therapy need to understand that adaptation to the ITB pump and proper dose titration can often take one year in order to obtain the best results. The ITB therapy alone is not nearly as efficacious as when combined with aggressive physical, occupational and speech therapy. Many motivated patients continue to make positive neurologic adaptations and changes for years after pump placement. Improvement in speech, swallow, motor function, bowel, and bladder function have all been found after ITB therapy [46]. For this reason, timing of initiating ITB is important in those who may be candidates for other types of surgery such as tendon lengthening, bladder surgery, or reconstructive orthopedic surgery [20, 38]. It is often helpful in adult patients to place a pump and optimize dose titration before these types of procedures are undertaken. This approach may differ significantly from approaches for pediatric management. Decisions regarding major equipment needs such as new orthotics or new wheelchair systems should be put off until after implantation of an ITB pump due to the fact that prescriptions for these devices may change with optimization of tone.

Special consideration is given to those patients with Multiple Sclerosis (MS) [44]. Requests for consultation regarding worsening spasticity and consideration of ITB therapy often occur in the context of rapid worsening of MS. Those with initiation of ITB therapy at this point will often blame the ITB therapy as the reason for inability to ambulate post operatively. These patients may have been overly reliant on tone rather than on intrinsic strength for gait and they also frequently experience continued MS exacerbation due to stress from surgery or natural course of disease. Clear discussion of realistic expectations and potential loss of motor ability should take place before ITB therapy is considered. There is a trend toward earlier implantation of ITB pumps in those with MS before a significant amount of ambulatory ability is lost. ITB therapy is also quite appropriate in the late stage MS patient with wheelchair bound status, both for comfort and caregiver ease.

Cognitive impairment in those with ambulatory ability can be problematic at times. New learning and memory are essential in making the most out of the combination of therapy and ITB. These patients are often poor historians, and when pump problems arise, management difficulties ensue. They may have poor coping skills which complicate the troubleshooting process. These patients cannot recall their functional performance pre-pump, and thus have a tendency to underestimate the benefit derived. Videotape of the patient's functional abilities pre and post pump placement can be very helpful for both the clinician and the patient for evaluation of ITB efficacy.

General management of the adult patient and pump

Management of the implanted intrathecal baclofen pump begins at the initial evaluation. Addressing and clarifying the patient's expectations is crucial. It is very important that the patient understands ITB therapy as a treatment and not a cure.

Intrathecal baclofen therapy takes time to reach the most therapeutic dosing possible for each individual. The patient must understand that the intrathecal baclofen therapy is only part of the picture. He or she must be willing to commit the time and energy it takes to work with the therapies prescribed to allow the changes and improvements to occur.

With most adult patients, initial dosing is set at 100 μg/day. This may need to be set lower if the patient was sensitive to the trial bolus dose. It is wise to start with a baclofen concentration of 500 μg/ml since it is unknown how high a dose the individual will need. Later, when the daily dose reaches over 200 μg/day the baclofen concentration can be increased. Dose increases of 10–20% initially are suggested until a therapeutic level is reached or the patient shows unacceptable side effects such as excessive drowsiness or urinary retention. Some conditions such as MS, require a conservative increase since these patients tend to be more sensitive to dose changes. Supplementing the patient with small doses of oral baclofen may be necessary until a therapeutic intrathecal dose is reached.

Spasticity can increase with an injury, infection, illness or even psychological issues such as stress or depression. The dosing regimen can be changed to fit the patient's needs. Bolus doses can be added to the continuous infusion mode at specific points of the day when

spasticity is increased. If the patient becomes tolerant to increases in daily dosing or if there are side effects to higher dosing, one can consider intermittent bolus dosing as an option. Intermittent bolus dosing gives the patient a scheduled bolus dose. Bolus doses are best set at either every 4 or 6 hours to accommodate the 24 hour clock.

Compliance is imperative with pump refill appointments. Pump refill appointments are set up approximately a few days before the low reservoir alarm date. A prescription of oral baclofen is necessary for the patient to have on hand in case of pump or catheter failure. If the patient complains of symptoms of withdrawal, immediate action must be taken.

Adult experience with ITB at University of Minnesota and Sister Kenny Rehabilitation Institute

The combined adult ITB pump experience between Sister Kenny Rehabilitation Institute and University of Minnesota Hospitals and Clinics represents over 300 ITB patients over 16 years. In our clinical experience we have found the following:

1. No matter how clinically appropriate the patient may be for ITB, inadequate coping skills or psychiatric problems have been difficult to manage in the clinic setting.
2. Educating the potential user of the pitfalls of ITB therapy through multiple discussions before a pump is placed results in a much smoother process if problems do arise. We discuss the potential for infection, catheter malfunction, drug withdrawal and overdose at length with these potential candidates in the clinic, at the dosing trial, and at the preoperative appointment so that patients and their families clearly understand the risks as well as the benefits.
3. Use of an experienced surgeon for implantation has been crucial in terms of managing complications. Our experience has been that those surgeons doing less than 12–15 implants per year or those with less than 50 total implants have a high rate of complications. We have had equally good luck with Neurosurgeons, Anesthesia Pain Specialists, and Orthopedic Spine surgeons as long as they are well trained.
4. Use of a team of therapists well trained in the expected changes following ITB placement has worked much better than utilizing a variety of therapists. We try to train one to two Physical, Occupational and Speech therapists who will essentially have a dedication to the program for our trial dosing tests and also our post operative rehabilitation. The physician works closely with these individuals to help with dose titration. If the patient is too weak to make rehabilitative gains following an increase in dose, the therapist will notify the physician's office to turn down the rate slightly. Conversely, if the tone remains too high to make gains, a dosing increase recommendation is often made by the therapist in order to facilitate optimum use of therapy sessions.
5. Once a pump is placed, an inpatient rehabilitation stay under the care of the ITB pump managing physician has been very valuable in terms of future clinic management of the patient, even if the stay is only for five days. Those who are completely independent in activities of daily living and mobility or completely dependent in these areas are not appropriate for an inpatient stay.
6. After the surgery, it is helpful to provide the patient with a supply of oral Baclofen and perhaps Cyproheptadine and Diazepam so that they have an emergency supply of medications to start if there are symptoms of ITB withdrawal. This will minimize their discomfort until reaching medical attention. We educate extensively on symptoms of withdrawal. Diffuse pruritis with increased tone is felt to be ITB withdrawal until proven otherwise.
7. Even though there are many diagnostic tests available to determine whether there is a malfunction of the ITB pump or catheter, there is no substitute for clinical judgment. We have had many cases in which multiple diagnostic tests do not show any pump abnormality, but the patient is clearly not having a benefit, despite significant dosage increases. Whether this has occurred as a result of micro tears in the catheter or kinking intermittently by patient position is often unknown. It is rare for the device itself to malfunction before the battery expires. However, replacement of a catheter is quite reasonable just on clinical suspicion alone, without supportive diagnostic tests, and usually results in success after catheter replacement. Placing the dose at the last known effective dose or lower is advisable with catheter replacement due to the potential for overdose.
8. We have had excellent results with early implantation in those with MS who are still ambulatory, even if the spasticity is subtle or only present dynamically with gait, and quiescent with rest. The ITB seems to have a very favorable effect on fatigue associated with increased work of ambulating with

excessive tone. Many of these patients will have increased fatigue with oral medications.

9. Those who are wheelchair bound or bed bound with needs to decrease tone for caregiver ease or for pain management tend to do very well with ITB.
10. Individuals who are very active or have very high tone tend to have more problems with catheter malfunctions.
11. The use of botulinum toxin and phenol blocks for remaining areas of focal tone that are resistant to the effects of ITB are still quite helpful and appropriate after pump implantation. Ankle plantar flexors and inverters, shoulder internal rotators, and wrist/finger flexors tend to be problem areas that may need more spasticity intervention than other parts of the body. We often only need to do a few injections post operatively if the patient is diligent in home exercise and orthotic use, and the gains made with the injections are often maintained by the ITB pump. There are often recalcitrant areas of tone in the upper extremities which may need ongoing treatment.
12. We have patients greater than five years post implantation who are still making functional gains through diligent exercise and remediation of old contractures and poor gait habits. We have a lot of success with heel cord lengthening after ITB placement in those with persistent knee recurvatum and other gait abnormalities related to plantar flexion contractures.

Indications and selection criteria for intrathecal baclofen use in pedicatrics

Interventions for hypertonicity are fairly limited for the pediatric population. Most of the medications that are commonly used have not been specifically researched for use in children and therefore they do not have FDA labeling for this use. Also, no single medication has been found to be effective to treat increased tone in all individuals [29].

As in adults, the mere presence of hypertonicity is not an indication for its treatment [30, 52]. It is essential to have goals that are anticipated to be achieved through its reduction. These goals may be to improve function, increase comfort, or make care provision easier. Also improved positioning can be an appropriate goal of tone reduction [30, 52]. It is important to consider whether or not tone is being used functionally. For example, an individual might be making use of their extensor tone in order to facilitate standing pivot transfers. If this is the case, tone reduction might negatively impact this ability.

It is important to eliminate potentially treatable conditions that can result in increased tone prior to considering the implantation of a programmable pump for the continuous delivery of intrathecal baclofen. Treatable causes of increased tone include urinary tract infections, pressure sores, fractures and dislocations, hydrocephalus, and nutritional status [51, 24, 52].

Intrathecal baclofen has been shown to be effective in the treatment of children with spasticity of cerebral and spinal origin [2, 4, 21]. Ideally, a multidisciplinary team including pediatric neurosurgery, pediatric rehabilitation medicine or neurology and pediatric orthopaedics should evaluate the child being considered for intrathecal baclofen. Screening by physical therapy and social work are also important [7].

Typically, the child for whom intrathecal baclofen is recommended has generalized tone increase that is not responsive to oral medications. This abnormal tone can be spastic, dystonic or a combination. It also interferes with function or the provision of care.

As increased tone is almost always responsive to intrathecal baclofen, it is not mandatory to perform a trial screening prior to implantation if other factors make it more complicated. These factors could include being post spine fusion or having severe scoliosis.

The child must be large enough to support a pump. The pump itself is about 7.5 cm in diameter. The thickness is determined by the reservoir size. Typically, a 15-kg child is large enough to accommodate the size of a pump. Nutritional factors are also important, as they must have sufficient subcutaneous fat to provide for tissue between the pump and skin and decrease the possibility of erosion of the pump through the skin.

As with any implanted device, there is a risk of infection with intrathecal baclofen pump systems. Although the frequency reported in the literature varies from 0–16%, it is generally thought that the risk is similar to that of ventriculoperitoneal shunt infection at about 5% [10, 25, 42]. The routine use of perioperative antibiotics is employed to decrease the likelihood of infection.

Catheter complications are the most frequently noted. The reported rate varies up to about 25%. These problems can include breakage, obstruction, disconnection of two piece catheters, and migration out of the intrathecal space. The catheter tip can become subdural or the entire catheter can migrate out of the intrathecal space and curl up behind the pump in the pocket that was created. Catheter problems can result in a variety of symptoms including periodic over and under delivery of

baclofen, acute withdrawal, or non-responsiveness to dose increases [6, 13, 22, 40, 47].

Since the most frequent diagnosis that ITB is used for in the pediatric population is cerebral palsy, its association with other conditions can affect the complications that are seen after pump implantation. For example, hydrocephalus is commonly seen in association with cerebral palsy. If a child has a ''compensated'' hydrocephalus at the time of pump implantation, they could be at risk for the development of a cerebrospinal fluid leak. This could be manifest as swelling by the back incision site or the pump site in addition to the other signs and symptoms of cerebrospinal fluid leak. Often the swelling will vary with position and be more prominent when the child is upright. This is logical in view of the increased hydrostatic pressure exerted on the area of catheter penetration of the dura when in an upright position. Additionally, children may stress the hardware in ways that adults are not likely to. Their greater range of back mobility might cause the catheter to be caught in between bony elements.

Pediatric experience with ITB at Gillette Children's Specialty Healthcare

Gillette Children's Specialty Healthcare has been using baclofen for the treatment of spasticity since 1993. The majority of those who are receiving this treatment are children with cerebral palsy. Those treated also include a number of adults with congenital or childhood onset disability. Other diagnoses include spinal cord injury, acquired brain injury, neurodegenerative disorder and spina bifida.

We have found that ITB is very effective. Of more than 400 ITB trials by lumbar puncture, only a very small number of those have not shown a significant decrease of spasticity. Of that small number, all who have returned for higher doses have had a positive response. We no longer require a trial of ITB prior to pump implantation in all cases. If there is a concern about the individual making use of his/her tone for function we are likely to do a trial infusion.

We have also found that failure to respond to oral baclofen is not predictive of whether or not ITB will be effective for the patient. Also, if the individual is on oral baclofen and still has high enough tone to consider ITB, it is not necessary to taper them off of the oral baclofen prior to a trial.

Dose has not been related to age or weight. We have also found that it generally takes a period of weeks to months to reach a stable dose, but once that dose has been reached little change is needed unless a problem with drug delivery has developed. Often, those with neurodegenerative disorders appear to require lower doses than those individuals with other causes of spasticity.

Our experience has been similar to those who have made reports in the literature. The most frequently noted type of complication has been catheter related. Over time, as surgeons increase their experience with the procedure and hardware and as the catheters have improved, we have seen a decrease in the frequency of catheter complications.

It is interesting to note that although ITB withdrawal can be a serious problem, it is not seen universally. Sometimes a catheter fracture will be noted as an incidental finding when X-rays are obtained for another reason. It is not possible to predict who will experience ITB withdrawal.

There has been a suggestion that ITB might increase the frequency and progression of scoliosis. This is difficult to evaluate, since those who receive ITB pumps are at high risk to develop scoliosis. There have not been prospective studies evaluating this and the 3 retrospective reviews have had different results and conclusions.

Satisfaction with this treatment has been high. The majority of those who have received pump implants at our institution function at Gross Motor Function Classification System Levels IV or V. Therefore, the pumps have generally been implanted to improve comfort or make the provision of care easier. Even when there have been complications, those with pumps usually request reimplantation or correction of catheter problems due to the benefits that they note when the ITB is being delivered. Some functional improvements have been noted with the use of ITB as well.

Pump problems and solutions

Baclofen systems, although well engineered, do at times fail. The failure to deliver Baclofen intrathecally to a patient who has been receiving baclofen in this manner exposes the patient to the possibility of baclofen withdrawal syndrome [16]. Baclofen withdrawal syndrome may lead to death and consists of the following symptoms: Spasticity, increased muscle rigidity, rhabdomyolysis, hyperthermia, hypertension, tachycardia, altered mental status, coma and/or seizures. This may mimic syndromes with similar presentations such as neuroleptic malignant syndrome and malignant hyperthermia and sepsis. It has been described that pruritis

may be a prodrome symptom to withdrawal with reasonable reliability except in patients with MS.

Because of the possibility of death, the clinician must be able to evaluate the pump/catheter system in a timely and efficient manner so that the delivery of the intrathecal baclofen can be reinstituted at the earliest possible moment. The delivery of baclofen intraspinally has been demonstrated to be the most reliable way to reverse the baclofen withdrawal syndrome and prevent death. Cyproheptadine, an H_1 antagonist as well as a 5-HT_{2A} receptor antagonist has recently been demonstrated to attenuate acute intrathecal baclofen withdrawal [39].

The patients in one small series responded to Cyprohiptadine with a decrease in fever (a drop by at least 1.5 °C.), heart rate from 120 to 140 to less than 100 bpm, associated with a decrease in spasticity, tone/myoclonus and itching. Symptom reduction was more pronounced with Cyproheptadine than oral dosing of either baclofen or benzodiazepines [16].

Certainly benzodiazepines, other sedative-hypnotics, antiadrenergic substances and even dantrolene sodium may still be helpful in modulating the symptoms of baclofen withdrawal, although not completely preventative.

Baclofen pump/catheter system failure can occur as a result of either failure of the pump or the catheter. Ten to forty percent of all implanted pumps involve system failure. In 70–90% of the cases of system malfunction the cause was catheter problems. Catheter complications include: Disconnect, kinks, obstructions, fractures, migration (either subcutaneous or subdural), granuloma formation or cerebral spinal fluid leak.

Uncommonly it is the pump, especially for those patients who are in well established baclofen pump programs. Pump problems include: Pump reservoir overfill, reservoir ''old'' baclofen, low residual volume or empty, internal catheter disconnection, exhausted battery/electronic failure [22, 48].

When a patient presents with increased spasticity, whether acute or not, the clinician must also consider other causes such as drug tolerance, disease progression, other co-morbidities such as urinary tract infection, small bowel obstruction, pneumonia, meningitis, nephrolithiasis, and others which increase nociceptive input and thereby increase excitation and spasticity [8, 9].

Initial evaluation involves interrogation of the system to assess correct programming. Certainly there have been instances of programming errors causing over/under dosing of baclofen. At the same time reservoir volume and battery life can be checked as well as when the last refill occurred which may indicate how ''old'' the baclofen solution is. In our experience, some patients with spasticity due to spinal cord injury have experienced a decrease in baclofen effectiveness when their baclofen solution is older than 60 days. It is also possible that the concentration of drug may be in error resulting in decrease baclofen dosing.

At the discretion of the clinician, if the reservoir volume is adequate (>4 ml), the reservoir may or may not be refilled with a ''new'' baclofen solution. Once the pump has been refilled, the pump is programmed to deliver a bolus dose of baclofen, (50 μg) to recheck the patient's responsiveness to baclofen. If the patient responds to the bolus as expected with a measurable decrease in spasticity, the system is assumed to be intact and the necessary adjustments in dose and/or mode of delivery are made at that time. The bolus dose usually peaks in three to four hours at which time other modes of system evaluation can be carried out.

Plain X-ray or fluoroscopy can be used to assess the pump and catheter. The pump motor can be programmed to conduct a 90° turn under fluoroscopy or serial plain x-ray before and after the reprogramming. At the same time, a survey of the catheter can be carried out to reveal disconnects, kinks, gross fractures or catheter migration. Our experience, as well as others in published reports, reveals these problems can occur despite an intact system appearance on plain X-ray/fluoroscopy.

Following clearance of the bolus dose the side port can be accessed, the catheter aspirated for cerebral spinal fluid. If cerebrospinal fluid is obtained, a radio-opaque contrast can be injected to look for catheter leaks or subdural extravasation at the catheter tip. Granuloma formation can also be detected with pooling of the X-ray contrast in a characteristic pattern around the catheter tip.

Other tests which might be helpful include radio isotopic evaluation with either T_C 99 m – DTPA or Indium-111 DTPA. This can reveal obstruction or fracture of the catheter [34, 41]. Alternatively, lumbar puncture can be carried out under fluoroscopy and cerebral spinal fluid samples can be withdrawn and sent to the lab to test for baclofen levels. At the same time, the lumbar puncture can be utilized to administer a test dose of baclofen should the programmed bolus via the pump/catheter system fail to produce a response.

The most common cause of failure to deliver intrathecal baclofen is still catheter failure. The improvement and re-introduction of the two piece catheter has decreased this number but failure still occurs. Despite a number of different ways to evaluate the system, catheter malfunctions are still a problematic diagnosis.

Ultimately, a high index of suspicion needs to be maintained in the presence of systems of increased spasticity and/a baclofen withdrawal. Even when the above evaluations are negative for system failure, empirical surgical replacement of the catheter usually solves the problem [11, 18].

Miscellaneous complications of cerebrospinal fluid leak are usually effectively treated with epidural blood patch performed under fluoroscopy [27, 45]. This is a complication which is detected in the perioperative period secondary to patient complaint of postural headache, nausea and vomiting.

System infections and/or meningitis were previously treated by pump/catheter explantation followed by a course of IV antibiotics [1]. Recent reports advocate leaving the system in place and placing antibiotic beads in the pump pocket and combining vancomycin with the baclofen for intrathecal administration [12, 53].

Vigilance is required in caring for patients with pump/catheter systems delivering intrathecal baclofen for spasticity control.

Future uses of baclofen pump therapy

Other medications besides baclofen can be delivered via the intrathecal method (such as clonidine and narcotics) and more medications are being evaluated. Some centers advocate a mixture of ITB with other medications for optimum pain and spasm relief; however, there are no significant studies for safety and efficacy of this practice.

Placement of the catheter tip for intrathecal baclofen is usually at the lumbar/thoracic levels. This is due to the possible side effects (respiratory distress and lethargy) from greater concentrations of baclofen when the tip is placed at the higher (cervical) level. However, a number of studies have shown that higher catheter tip placement has been both safe and effective for the treatment of patients with spasticity and dystonia [14, 17, 31].

Measurements of the drug concentration in the cervical region with different cervical catheter placements may help determine if a catheter tip at the C1–C3 level delivers a significantly greater drug concentration (at a lower total dose) as compared with the C5–C6 or C8–T1 level [19].

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Intrathecal baclofen therapy in patients with severe spasticity

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Summary

Spasticity has been described as "a motor disorder, characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron syndrome". In patients with complete spinal cord lesions, severe untreatable spasticity can make movement, sitting and hygiene difficult or impossible while it may alter gait and personal care in patients with partial lesions. From a clinical point of view, it is useful to distinguish spinal cord spasticity from supraspinal spasticity. Traditionally, the Ashworth scale is the most widely used to quantify the tone of single muscles. In order to quantify hypereflexia, the Reflex Scale is also used. In the spinal spasticity which is characterized by spasms, the Spasm Frequency Scale is useful in order to monitor their frequency. Initially, management of spasticity is based on non-invasive treatments that later become more invasive. The first approach, the conservative treatment, usually includes elimination of the nociceptive stimuli, rehabilitative therapy (physical and occupational), orthopaedic prostheses and plaster corsets. These treatments, do not resolve spasticity in about 33% of cases. In these severe cases, more invasive procedures such as muscle infiltrations with botulin toxin and intrathecal baclofen infusion can be used.

Keywords: Spasticity; baclofen; intrathecal.

Spasticity

Spasticity has been described as "a motor disorder, characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron syndrome" [11]. Clinically, spasticity is characterized by hypertonus, hyperactive reflexes upon muscular extension and abnormal spinal reflexes (synkinesia, clonus, Babinski sign). In some cases, it is possible to observe clonus and muscular spasms [7]. In patients with complete spinal cord lesions, severe untreatable spasticity can make movement, sitting and hygiene difficult or impossible while it may alter gait and personal care in patients with partial lesions [1]. It may be the cause of pain, contractures, fractures, bed sores, limited independence of functionality and deteriorated quality of life.

From a clinical point of view, it is useful to distinguish spinal cord spasticity from supraspinal spasticity. Spinal cord spasticity includes loss of the supraspinal inhibition, loss of segmental inhibitory neurons, and sprouting of collateral fibres and alteration of muscle fibres. When spasm frequency and intensity increase (painful due to synkinesia and subclonic reflexes), there is a marked Babinski sign and a higher frequency of hypereflective bladder. It is associated with multiple sclerosis, traumatic lesions, or other pathologies of spinal cord like familiar spastic paraparesis, medullary tumors, cervical spondolytic myopathy, transverse myelitis, lateral amyotrophic sclerosis, neurofibromatosis and lupus myelitis [1, 2]. Supraspinal spasticity usually appears when the segmental control of the spinal cord has been lost [11, 7] due to a lack of descendent impulses that normally stimulate release of inhibitory neurotransmitter γ-aminobutyric acid (GABA), which acts at the presynaptic level inhibiting the release of excitatory neurotransmitters [1]. Clinically, with respect to spinal spasticity, hypertonia prevails on the hyperreflexia and clonus, synkinesia and pathological reflexes. This type of spasticity occurs in cerebral palsy (lesion acquired before or during birth or within the first five years of life, often with athetosis, chorea, dystonia and ataxia [8, 9] and in traumatic, vascular, tumoral, and infective cerebral lesions.

Spasticity assessment scales

Traditionally, the Ashworth Scale is the most widely used to quantify the tone of single muscles: $1 =$ no increase in muscle tone; $2 =$ slight increase in tone giving a "catch" when affected part is moved in flexion or

extension; 3 = more marked increase in tone but affected part is easily flexed; 4 = considerable increase in tone; passive movement difficult; 5 = affected part is rigid in flexion or extension. When assessing a patient, the scale should be administered by two different people so as to compare the two results. In order to quantify hypereflexia, the Reflex Scale is used as it can be applied to every single reflex: 1 = absent; 2 = weak; 3 = normal; 4 = lively; 5 = excited; 6 = subclonic. In the spinal spasticity characterized by spasms in order to monitor frequency, the Spasm Frequency Scale is usefull: 0 = no spasm; 1 = stimulation induced spasms; 2 = less than 1 spasm an hour; 3 = more than 1 spasm an hour; 4 = more than 10 spasms per hour. These three assessment scales measure segmental not functional spasticity. The results of these scales however do not tell us what the patient truly does during the day. In a modern rehabilitative approach, however, it is important to use scales that measure spasticity as a disability in order to assess improvement in quality of life. Scales such as the Expanded Disability Status Scale (EDSS – for multiple sclerosis patients), Functional Independence Measurement (FIM) and Barthel Index (BI) can be used. An experimental attempt for measuring spasticity objectively using bioengineering in movement analysis (personal data) or the ''soleus stretch reflex'' has been made [14].

Spasticity treatement

The first approach to spasticity is usually a conservative treatment, like elimination of the nociceptive stimuli, rehabilitative therapy (physical and occupational), orthopaedic prostheses and plaster corsets. The patient can also be treated with oral antispastic drugs like baclofen (25–125 mg/die), oral tizanidine (4–12 mg/die), gabapentin (300–1800 mg/die). Diazepam (10–20 mg/die) can be used intramuscularly. Dantrolene is no longer used [24]. Notably, a positive effect is described with cannabinoids [23]. These treatments, in about 33% of cases, do not adequately resolve spasticity. More invasive procedures such as muscle infiltrations of botulin toxin, intrathecal baclofen infusion, and muscular infiltrations of phenol are needed [8, 2]; doubtful is the use of intrathecal phenol [10]. Presently, there is a tendency towards invasive therapies; i.e. orthopaedic and musculoskeletic surgical procedures that permit to lengthen tendons and muscles, or neurosurgical selective posterior rhizotomy to reduce tension, pain and spasticity [4].

Severe untreated spasticity does not only influence the patients but all those who assist them, thus increasing the medical assistance and socio-economic costs. These patients suffer pain and severe limitations in mobility and function with consequent reduction of social and work activities. This leads to poor quality of life [5] and in some cases depression. The health team often faces major difficulty in offering assistance; external urinary catheterization is one common troubling problem. Total health costs for medical assistance increase due to treatment of complications related to spasticity, such as fractures, dislocations, and bed sores.

Pharmacokinetics of oral versus inthrathecal baclofen

Baclofen, is the major drug used in spasticity. It is a γ-aminobutyric acid (GABA) agonist, inhibitor. The drug acts specifically on the GABA-B receptors [2]. At the level of the spinal cord, it inhibits the absorption of calcium that prevents the release of excitatory neurotransmitters which play an important role in spasticity. Physiological studies indicate that baclofen acts at the presynaptic level, where it reduces the excitability of motor neurons inhibiting the release of excitatory neurotransmitters. If present at higher levels in the cerebrospinal fluid (CSF), it can also act at the postsynaptic level antagonizing the activity of the excitatory neurotransmitters. It is characterized by poor liposolubility and does not cross efficiently the blood brain barrier. Consequently, even at high doses, oral baclofen reaches relatively low levels in the CSF, inhibiting spasticity in a very limited way. At the same time, the high blood levels due to oral administration can induce unpleasant side effects in the central nervous system such as sedation, sleepiness, ataxia, and respiratory and cardiovascular depression.

On the contrary, baclofen administered directly in the intrathecal space, can guarantee a safe and efficient treatment, able to reduce spastic hypertonia and spasms, because it acts directly on the GABA-B receptors of the spinal cord, while the side effects associated with the high doses of oral baclofen are minimized. Patients treated with 400 μg/die of intrathecal baclofen, have markedly higher levels of the drug than patients treated with 100 mg of the same drug (380 ng/ml vs. <12–95 ng/ml) [12]. Moreover, the blood levels of intrathecal baclofen remain very low (<5 ng/ml). Schematically, we can state that with respect to oral administration, intrathecal administration induces levels at least four times superior in the CSF with 1/100 of the systemic dose. Blood levels as well are 1/100 with respect to those observed in oral baclofen. The pharmacological concentration of

baclofen in the CSF compared to this in the blood is very high. In fact intrathecal administration concentrates baclofen in specific receptorial sites of the spinal cord. This warrants efficacy and limited side effects in the central nervous system.

History of intrathecal baclofen therapy in the control of spinal and supraspinal spasticity

Intrathecal baclofen was used for the first time on guinea pigs in 1978 by Wilson [25], who observed a decrease in nociceptive reflexes. The efficacy of intrathecal baclofen in man for the control of spinal cord spasticity was described for the first time by Penn *et al.* in 1984 who administered baclofen in the lumbar subarachnoid space as a single intrathecal injection and reported a transitory reduction of spinal cord spasticity. In 1985, Penn *et al.* reported a decrease in spasticity after continuous intrathecal infusion of baclofen [18] and in 1989 they demonstrated the positive results of a double blind study on the effect of intrathecal baclofen (ITB) therapy in 20 adults with spasticity due to multiple sclerosis or spinal cord lesion [17]. The latter study demonstrated a decrease in Ashworth scale scores in the lower limbs from 4.0 to 1.2 after treatment, with a concomitant attenuation of muscular spasms from 3.3 to 0.4. These and other studies demonstrated that ITB gives a relatively safe control of spasticity. Many patients described that the reduced spasticity permitted them to have a major ''perception of their body'', while an excessive reduction resulted in ''weakness''.

Ochs, from Monaco, strenghtened Penn's case by carrying out a multicentered study on the long term treatment of spinal spasticity by ITB [15], and the Austrian school of Innsbruck demonstrated treatment efficacy even in supraspinal spasticity (brain trauma) [20–22]. In 1989, after a 5 year experiment, a programmable ITB pump was produced in the United States. In June 1996, after several years of monitoring in several European centres, (including our group, which since 1990 collaborates with Innsbruck), ITB therapy was approved by the Food and Drug Administration (FDA).

Patient selection

Selection and screening of patients is a fundamental procedure before beginning intrathecal baclofen therapy (Table 1). In order to understand the complex relationships between spasticity and daily functions the patients undergo multidisciplinary assessements from a neurologist, physiotherapist, neurosurgeon, psychologist, anaesthetist and if necessary from a orthopaedic surgeon. A social assistant is usually present during these assessments.

Table 1. *Inclusion criteria for an intrathecal baclofen in spasticity at the IRCCS Centro Neurolesi, Italy*

1. No hypersensitivity or allergy to baclofen
2. No age limits, but above 65 years of age, rehabilitative advantage and risks should be very precisely assessed
3. Diagnosis confirmed
4. Spasticity chronic and severe (Ashworth scale average >3.5; duration >12 months)
5. Spasticity refractory to orally administered drugs or patients have had undesirable side effects with the orally prescribed dosage
6. Normal cerebrospinal fluid flow
7. The patients should have no programmable medical devices such as pacemakers
8. Fertile women should take contraceptives because a pump would make pregnancy very risky
9. No severe pathologies such as cardiac, respiratory, renal and hepatic diseases
10. Caregiver has a clear idea of the immediate rehabilitative goals (1 year), median (5 years) and long term (over 5 years)
11. Patient signs an informed consent that therapy is symptomatic and not curative
12. The response to an intrathecal bolus test of baclofen is positive

Rehabilitative goals

The rehabilitative team should check if reduced spasticity improves functionality or makes the patient's care assistance easier. The patient, family and caregivers should therefore be consulted with regard to the true functional goals, nursing and assistance. In patients who expect functional improvement, the goals should include a good level of independence and reduction of pain. The goals of other patients can instead be comfort, easier assistance, and posture maintenance, adequate perineal hygiene, which is often extremely difficult in cases of severe adductor hypertonia of the hips, and the prevention of further contractures, tendineous retraction and bed sores.

Screening test

Patients undergoing screening should interrupt all drugs that depress muscle tone (baclofen, etc) 48 hours before the test. When possible, it is preferable to interrupt all drugs that can potentially depress the central nervous system. Oral baclofen should be withdrawn gradually in order to avoid any possible, even rare, appearance of hallucinations (case history from personal records). In patients with prevalent spinal cord spasticity,

a 25 μg intrathecal bolus, is injected through a lumbar puncture. Baclofen solutions of 50 μg/ml are used. Cardiac and respiratory function as well as blood pressure, and level of alertness are monitored. If response is positive, we begin to observe a significant reduction in Ashworth scale scores, without side effects 2–4 hours after bolus administration. The maximum response is registered, in our experience, after 4–8 hours and gradually disappears after 12–16 hours. When absence of side effects is observed without a significant reduction in Ashworth Scale scores, we repeat every 24 hours a boluses of 50–75–100 μg. Larger boluses are not usually administered in patients with spinal cord spasticity. In patients with severe supraspinal spasticity the initial bolus is increased from 50–100 μg gradually to 200 μg.

Implantation

Patients should have no bed sores or other infections at the sites involved in pump implantation. Site of pump implantation is assessed and decided before surgery according to the condition and physical characteristics of the patient. The procedure is usually carried out under local anaesthesia. The patient is placed in the lateral decubitus position. In case of marked supraspinal spasticity, general anaesthesia is used. This becomes necessary in particular clinical conditions that force the patients in hyperextension of the trunk making insertion of the lumbar needle difficult.

A small median cutaneous incision is carried out at the level of the L3–4 space. A Tuohy needle is inserted between the two vertebrae and a thin walled spinal catheter with a closed tip and six lateral holes is pushed through up to the T10–12. Positioning is checked using a brilliance intensifier. The lumbar incision is then lengthened by a few centimetres in order to allow the connection and anchorage of the catheters. A semi-circular incision is then carried out in the epigastric area. A thick walled abdominal catheter is connected to the spinal one through a tunnel. After making sure that CSF is flowing, the catheter is connected to the pump which is then inserted in a subcutaneous pocket in the epigastric area and fixed with stitches to the underlying muscular fascia.

The last generation device for intrathecal infusion is composed of a peristaltic titanium pump (87.5 mm by 19.5 mm, weighting 165 gr). The pump has a special fixing device to avoid dislocation or bending. It is powered by a lithium battery with a life expectancy of about 7 years (the larger the dosage, the more the pump works, the faster the battery gets depleted). At the end of this period, the pump is substituted under local anaesthesia using the same catheter. The catheter and the mechanisms inside the pump are radiopaque, while covering is radiolucent. This allows a first level radiological check in case of malfunction. The second level check is the injection of radiopaque contrast through the side port of the pump for diagnostic reasons. The third level is visualization of the rotation of the pump motor after an appropriate bolus administration in cases of suspect mechanical malfunction. When carrying out an MRI, the reservoir is emptied of baclofen and the pump is turned off in order to avoid accidental bolus. The pump is reactivated at the end of the MRI session. During the implantation or pump change, antibiotic and analgesic therapy as well as prophylactic low molecular weight heparin therapy are prescribed in order to minimize the risk of infection, venous thrombosis and pulmonary embolism.

Dose adjustment

Post-implantation, infusion depends on the dose that was efficient during the screening test. Maximum effect is obtained in the first 60 days after implantation. The dose is never increased in the first 24 hours after the procedure to make sure that there is no interference with the non-eliminated anaesthetic drug. From the 2nd day on, the dose is increased daily by 10–30% (in children by 5–15%), until the optimal dosage and effect are reached. The pump automatically calculates the baclofen dose to administer, when activated by the system, to fill the connection catheter. The criteria for the adjustment of dosage are: efficient suppression of ''reflexes'' (tendinous reflexes, muscular clonus, spasms, cramps and Babinski sign) and the decrease in muscle tone. The response to the various dose corrections is usually observed after 4–6 hours. In the presence of spastic alterations, it is advisable to investigate whether they are caused by pathological evolution or by drug-pump-catheter dysfunction.

Patients with progressive multiple sclerosis sometimes have modifications of spasticity during the day. If this happens on a somewhat regular basis, it is possible to ''personalize'' the infusion via the software furnished with the pump. The programs include continuous (the most frequently used), continuous-complex (a continuous dose bolus with boluses are programmed at fixed hours), single bolus, and periodic bolus. In brain-injured patients with reactivation of the nervous circuits, spasticity sometimes improves to the point that the therapy with ITB is no longer needed. In these cases the pump is

removed. Other conditions that may potentially need dose adjustment include tolerance to the drug, obstacles of flow or diffusion, such as fibrosis, possible latent manifestations of the pathology and the development of a concomitant disease.

The drug concentration initially used is 500 μg/ml and reaches a dose of 100 μg/die. Theoritically, it is possible to raise the dose to a concentration of 2000 μg/ml. However, we hope that the concentration adjustment comes about gradually. This happens because of the persistence of the precedent concentration in the catheter; until this is completely substituted by the new drug concentration, there is a transitory increase of spasticity in the patient. The new pumps allow to calculate an adequate bolus on the basis of variation of concentration. Moreover, for stability reasons of baclofen within the pump, the refills should be carried out maximum every 6 months; for this reason it is useless and costly to go to a concentration of 2000 μg/ml with the theoretic possibility to have the next refill after 12 months. Overall, the dose efficacy of ITB in spinal spasticity is half the one necessary in supraspinal spasticity. In spinal spasticity, the median dose in various studies varies from 298 μg/die to 900 μg/die. In our experience, in patients affected by multiple sclerosis, the median dose is 435 μg/die 2 months after implantation, higher than in spinal trauma or in Stumpell-Lorrain disease (285 μg/die), but lower than in brain trauma (612 μg/die). This, indirectly, confirms that spasticity in patients with multiple sclerosis is predominantly but not exclusively spinal.

Refilling

At the time of pump implantation, the patient's clinical data are entered with the use of a palm computer. The special software also shows the date of drug exhaustion and turns on an acoustic alarm for battery exhaustion. Furthermore, the pump has a ''side port'' used for diagnosis and for the administration of a second drug directly into the catheter bypassing the reservoir. The 20 ml reservoir has an external central access which represents the principal and most commonly used pathway. This hole is covered by a special silicone gum that allows a needle to go through 500 times without leakage or risk of contamination of pump contents. The ''refilling'' is carried out through a special kit composed of a special needle, a filter, a guide to the central hole, and a nipper to stop the air from entering the pump.

Before refilling the pump, the residual amount of baclofen must first be extracted. A printing system permits to check and file the paper copy as well as furnish the patient with an instant report.

Effects of intrathecal baclofen

The percentage of efficacy reported in the literature is superior to 30%. Clinically, it is possible to distinguish 3 categories of patients and their response to intrathecal baclofen:

1) patients with spastic paraparesis partially able to walk or able to stand, who complain of muscular spasm, pain and/or exaggerated muscular tone that interferes with movement;
2) patients with spastic paraplegia who complain of invalidating muscular spasms, pain or extremely exaggerated muscle tone; these patients are not able to use a wheel chair and have a limited quality of life.
3) para- or tetraplegic patients in an advanced chronic state of disease.

The patients of categories 1 and 2 experience the major functional benefits from ITB therapy, reaching a better level of mobility and independence. A significant improvement can also be the use of a wheelchair. Many patients succeed in doing professional and social activities after ITB. In the first category, it is more difficult to adjust drug dosage. Finding the right balance for walking or standing and decreased spasticity is more time-consuming. Even proposing ITB is difficult in this category of patients because during disease evolution the patient will have to choose whether to walk with spasms and reduce or block pump infusion or whether to maintain ITB and sit in a wheel chair. It is important to be clear when addressing the patient, family, and caregivers. In our experience a patient-physician relationship based on trust and knowledge is very important, because the final decision is taken by the neurologist who is in charge and manages his caregivers.

Penn [18] showed a decrease in Ashworth scale scores from 3.8 ± 0.7 before treatment to 1.6 ± 0.8 after treatment ($p < 0.001$). ITB also reduced both intensity and frequency of the spasms from 2.8 ± 0.7 to 1.0 ± 0.7. In our experience, in a group of 13 patients affected by progressive multiple sclerosis, we observed a decrease in Ashworth Scale scores from 3.5 ± 0.7 to 1.4 ± 0.6 ($p < 0.001$), in the Reflex Scale from 5.4 ± 0.8 to 3.5 ± 0.5 ($p < 0.001$) and in the Spasm Frequency Scale (SFS) from 2.8 ± 0.4 to 0.5 ± 0.2 ($p < 0.001$) (2 months after pump implantation). The overall variations that are not closely tied to the ''segmentary'' decrease of spasti-

city, were assessed with the Barthel Index, the FIM and the EDSS. The average Barthel Index increased significantly from 28.8 to 51.2 ($p<0.001$). Close examination of various items, shows a significant increase in FIM (36 to 60) ($p<0.001$). ITB efficacy in EDSS (from 5,8 to 5.1 with $p<0.01$) does not adequately assess bladder function when quantifying disability. Moreover, 90% of the patients suffering of ''pressing incontinence'' no longer had problems. Dose adjustment can be troublesome because drug increases may induce urinary incontinence before there is an acceptable decrease in spasticity. Interestingly, the improvement of detrusorial hypereflexia, in patients with spasticity of supraspinal origin such as patients with brain trauma [20], suggests an action on the micturition pontine centre. Treated patients who underwent urodynamics often show an increased bladder capacity, a reduced residual volume, and a small number of pelvic spasms, decrease or disappearance of pain and spasms improved duration and quality of sleep. In agreement with most scientific publications, we observed an improvement of scale scores for quality of life of these patients.

In *our experience*, at a five year follow-up, no real tolerance can be shown; however after a few years of continuous infusion most patients respond better to periodic bolus infusion or continuous complex infusion. In progressive multiple sclerosis we observed an increase in the average Ashworth Scale score (1.4 at one year from implantation, to 3.0 at 5 years from implantation). Dosage increase only partly succeeds in filling the gap (2.2). One year after implantation, the average dose of intrathecal baclofen is 435 g/die and at 5 years 620 g/die [3, 19].

Noteworthy are the findings in the other two categories of patients: a) in spinal trauma, ITB dose is substantially stable being 1.4 with 300 g/die at one year from implantation and in 1.6 with 340 g/die at 5 years from implantation, and b) in brain trauma, the dose is reduced (1.8 with 610 g/die at 5 years from implantation) and pump removal is possible in a few cases for functional recovery (Table 2).

Table 2. *IRCCS Centro Neurolesi spasticity patients treated by ITB*

Nr.	Patients	Age	Sex	Diagnosis
1	AG	70	m	syringomielia
2	MS	60	m	spinal cord injury
3	FA	42	f	myelitis
4	RA	64	m	Strumpell-lorrain desease
5	CN	7	f	cerebral palsy
6	FR	32	m	spinal cord injury
7	TC	49	f	Strumpell-lorrain desease
8	SC	57	m	spinal cord injury
9	LS	26	m	head trauma
10	FS	17	m	cerebral palsy
11	PL	32	f	head trauma
12	NM	63	m	multiple sclerosis
13	SL	11	m	cerebral palsy
14	PG	26	m	spinal cord injury
15	AF	63	m	multiple sclerosis
16	AM	42	m	myelitis
17	DM	14	f	cerebral palsy
18	SD	19	m	cerebral palsy
19	DA	53	f	multiple sclerosis
20	DC	38	f	multiple sclerosis
21	GA	44	m	cervical canal stenosis
22	TG	45	m	multiple sclerosis
23	UA	16	m	cerebral palsy
24	FD	46	m	spinal cord injury
25	LD	77	m	cervical canal stenosis
26	BS	36	m	spinal cord injury
27	AP	69	m	spinal cord injury
28	RA	63	m	Strumpell-lorrain desease
29	MS	39	m	spinal cord injury
30	ZF	52	f	cervical canal stenosis
31	MB	56	m	multiple sclerosis
32	AT	32	f	cervical canal stenosis
33	AE	65	m	cervical canal stenosis
34	CL	49	m	spinal cord injury
35	DM	26	m	spinal cord injury
35	GE	10	m	cerebral palsy
36	MA	35	f	head trauma
37	PC	66	f	multiple sclerosis
38	RE	65	f	multiple sclerosis
39	RF	36	f	head trauma
40	SF	27	m	head trauma

Side effects and complications

Complications and side effects are sufficiently described in scientific articles (Table 3). In 1995 a new thick walled catheter was introduced; this reduced drastically (<1%) all the complications related to the catheter. Adverse effects are rare during continuous treatment,

Table 3. *Complications of ITB for spasticity (according to Coffey et al. (1993) J Neurosurg 78: 226–232)*

- Mechanical dysfunction of the pump: 1%
- Cutaneous erosion on the pump pocket: 1%
- Infection of the pump pocket: 1%
- Twisting of the catheter: 7%
- Dislocation of the catheter: 8%
- Disconnection of the catheter: 6%
- Occlusion of the catheter: 1%
- Respiratory depression: 1%
- Hypotension: 1%
- Epileptic seizures due to baclofen: 1%
- Temporary tiredness: 1%
- Depressed humor: 2%
- Vertigo: 1%
- Meningitis after pump refill: 1%
- Overdose (with coma): 1%

but could include sleepiness, instability, constipation, and muscular hypotonia. Penn, in a retrospective study on 66 patients with spinal cord spasticity, treated for a period of 7 years, realized that the only procedure necessary was dosage reduction [17]. Overdose symptoms, even if rare, were due to administration of non-appropriate bolus, to variations of drug concentration or reprogramming of the pump. Symptoms included weakness, areflexia, hypotonia (with cranio-caudal progression), hypotension, respiratory depression, light-headedness, instability, convulsions, sleepiness, and in some very rare cases, death. A 2 mg dose of physostigmin is administered i.v.; this is a drug capable of inverting respiratory depression and sleepiness. Tolerance to intrathecal baclofen has never been confirmed. Some authors however, have treated the ''suspect'' tolerance by interrupting baclofen for a variable period from patient to patient (3–37 days) and administering, intrathecal morphine or hydromorphine. In all cases, the ITB treatment was continued with success and in a few patients, at an inferior dosage with respect to the one before withdrawal [7]. The abrupt withdrawal of it can induce rebound spasticity, motor hyperactivity, headache, sleepiness and/or disorientation, insomnia and/or hallucinations, convulsions and fever. In our experience, we had only one catheter dislocation.

Costs and final considerations

An immediate analysis of a therapy programme with intrathecal baclofen, calculating average pump substitution and four refillings per year gives a average yearly cost of about €4.000,00. In Italy, there are no adequate multicentered studies on the real savings resulting from an ITB program. Nance [13] calculated an annual saving of $25.520 CND per patient, due principally, to reduced hospital care. Ordia [16] observed an average reduction of 2.7 days in hospital care for every patient treated with ITB in the first year after implantation with a saving of $6.750 USD per patient. The same author calculated that screening costs and implantation were absorbed within 2.5 years. All this has led us to consider and evaluate an ITB programme on a long-term prospective.

Nonetheless, in Italy, there is a greater diffusion of ITB therapy. ITB should be managed, however, by highly specialized personnel with a great experience on the subject. Patient selection, dose adjustment, integration of ITB in the rehabilitative programme, prevention of complications, and pump-catheter problem solving are more difficult than we think. We can state that in patients with severe spasticity who no longer respond to conventional therapy, intrathecal baclofen can be a good treatment as a part of their rehabilitative programme.

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Intrathecal antispastic drug application with implantable pumps: results of a 10 year follow-up study

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Summary

Since 1986, more than 300 patients received an intrathecal baclofen (ITB) pump for the treatment of severe spasticity. Chronic ITB administration is a safe and effective method, which significantly decreases pathologically exaggerated muscle tone and improves the quality of life in most patients. This therapy is indicated in severe spasticity of cerebral or spinal origin that is unresponsive to oral antispastic medications. It is also useful in patients who may experience intolerable side effects when they receive orally effective baclofen doses. The therapeutic dose required to treat spasticity of cerebral origin is about three times higher than in spasticity of spinal origin. In carefully selected patients who suffer from spasticity, pump implantation is a cost-effective treatment which improves their quality of life. In our series with a follow-up period of 10 years, the ITB dose remained constant and no development of tolerance was observed in most patients. Destructive procedures such as myelotomy are no longer performed in our department in order to treat spasticity.

Keywords: Neuromodulation; spasticity; baclofen; programmable pumps; ITB.

Introduction

The term ''spasticity'' describes a motor disorder characterized by velocity dependent increases in tonic stretch reflexes and hyperexcitability of the stretch reflex. Spasticity represents a clinically important component of the ''upper motor neuron syndrome''. The most frequently used scale to evaluate the degree of spasticity is the Ashworth scale (see chapter on spasticity of cerebral origin in children by Sgouros (S)), which was described by Bohannon and Smith in 1987 [3, 8]. In this scale, the increase in tone and the resistance to passive movement is ranked from ''0'' being no increase in tone, to ''4'' when the affected parts are completely rigid in flexion or extension.

In the last 100 years, a variety of invasive and destructive procedures including myelotomy have been performed in order to treat spasticity when medical therapy was no longer efficacious [37–40]. In Germany, a multicenter study concerning ITB administration started in 1974 [13, 16, 25, 26]. Baclofen acts as gamma-amino butyric acid (GABAb) receptor agonist [7, 8, 11, 12, 20, 21, 31]. The mechanism of action is probably presynaptic and involves inhibition of calcium release into presynaptic terminals, thereby impeding the release of excitatory neurotransmitters. Many clinical studies have shown that baclofen is a potent inhibitor of spinal synaptic reflexes [1, 2, 4–6, 9, 15, 18, 19]. ITB reduces muscle tone in patients with spasticity of spinal or cerebral origin [22–24, 27–36, 41]. The effects are maintained over more than 10 years without the development of significant drug tolerance [10, 17]. ITB administration may be indicated in patients with spasticity grades 3–4 on the modified Ashworth scale; this represents a considerable increase in tone that makes movement very difficult. Similarly to the intrathecal application of opioids, the aim of ITB in intractable spasticity is to bring sufficiently high concentrations of the drug in proximity to the target organs, and simultaneously minimise the administered dose and the associated side effects. The oral and the intrathecal administration of baclofen have an inverse distribution pattern (Fig. 1). With programmable pumps, constant baclofen levels can be obtained in the CSF. In some patients, it is beneficial to program circadian drug cycles with lower baclofen levels during the day for physical therapy and mobilisation, and higher baclofen levels during the night in order to minimize spasm-related pain.

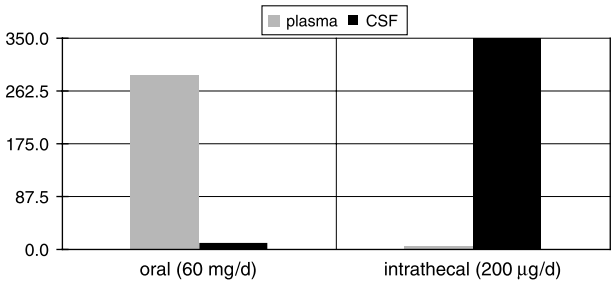

Fig. 1. Average plasma and CSF levels (mg and µg/d) after oral (60 mg/d) or intrathecal (200 µg/d) baclofen application. This inverse distribution pattern explains the relative low rate of systemic side effects of chronic intrathecal baclofen administration

Results of intrathecal baclofen application

At the Department of Stereotaxy and Functional Neurosurgery in Cologne University, ITB has become a standard therapy for severe spasticity. Destructive procedures such as myelotomy are no longer performed in our clinic. Since 1986, more than 300 patients were implanted with a pump for ITB administration. In the period 1986–1995, 252 patients were operated on and their follow-up exceeds the 10 years (Table 1). Of these patients, 63% suffered from spasticity of spinal origin and 37% from spasticity of cerebral origin. The most common diagnoses were multiple sclerosis (140 patients), posttraumatic damage (58 patients), and cerebral ischemia or haemorrhage (46 patients). The contraindications to ITB therapy in our clinic included problems such as uncontrolled seizures, anti-coagulation, infection, pregnancy, impaired renal function and autonomic dysreflexia. Before programmable implantable pumps such as Synchromed (Medtronic Inc., Minneapolis, USA) became available, the therapeutic effect was tested, after intrathecal catheter implantation, with a baclofen bolus of 50–100 µg; the titration was based on clinical examinations and was performed via an external pump. Only after a trial baclofen administration (usually for 7 days with the external pump) was successful, a permanent pump was implanted. Fully programmable implantable pumps are currently available; therefore, implantation of the catheter and pump can also be performed in one stage.

Table 1. *Causes of spasticity in patients treated by ITB administration at the Department of Stereotaxy and Functional Neurosurgery, Cologne University (1986–1995)*

Cause of spasticity	Origin of spasticity	
	Spinal	Cerebral
Multiple Sclerosis	140	–
Trauma	30	28
Degenerative	10	10
Ischemia	2	25
Tumor	6	3
Cerebral palsy	–	11
Total ($n = 232$)	*155*	*77*

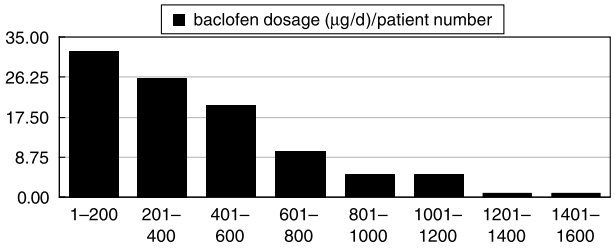

Fig. 2. Distribution of intrathecal baclofen dosage in 102 patiens with severe spasticity (Ashworth scale score: 3–4)

In all patients, a significant beneficial effect on spasticity was observed. Responders were defined as those who experienced an average reduction of 1.0 on the Ashworth scale in the lower extremities. The reduction of muscle tone was dependent on the daily dose. The required average therapeutic dose was much higher in cerebral spasticiy (860 µg) when compared to spinal spasticity (280 µg). In 102 randomly selected patients, we studied the distribution of baclofen dosage and we found that there was a wide range of the required therapeutic dose from 50 to 1600 µg/d (Fig. 2).

We observed an increase of the dosage during the first twelve months; this was dependent on the grade and origin of spasticity. We call this phenomenon ''adjustment time'', and we do not consider it a true tolerance. True drug tolerance to ITB therapy is not common; in fact, it is less than 1%. A ''drug holiday'' and substitution of baclofen with intrathecal morphine (1 mg/d) prevents the symptoms of withdrawal. Usually, baclofen therapy can be started again at a lower dosage after a baclofen-free interval of 5–28 days. The spasticity of the lower extremities responded much better than that of the upper extremities. In 232 patients, adjustment of the baclofen dose was necessary during the follow-up period, of 10 years. The number of refills was above 2000 altogether in these patients. There were no signs of tolerance during the follow-up period. Acute deterioration or resistance to therapy was due to technical complications in most cases such as dislocation, disconnection or obstruction of the cathether. In general, the rate of implant-related complications was 7% in the long-term (>3 years) follow up. The implant-related complications were: catheter dislocations (3), catheter rupture (1), malfunctioning pump (1), and pump rotation (1) in a very adipose patient (Fig. 3). Three patients

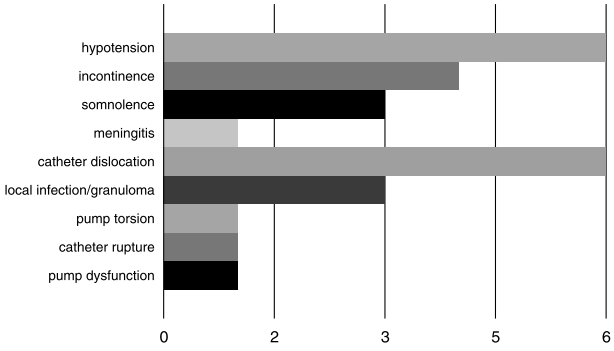

Fig. 3. Complications and side effects of long-term intrathecal baclofen application in 232 patients with a follow-up longer than 10 years. Number of implantations performed: 232, Number of pump refills: over 2000

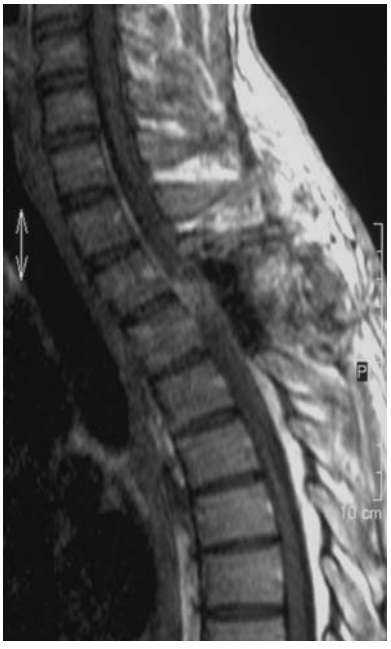

Fig. 4. T1-weighted contrast enhanced MRI shows the formation of an intraspinal granuloma at the level of the 7th thoracic vertebra, a rare complication of chronic intrathecal baclofen administration

became somnolent temporarily due to drug overdose. The pump had to be removed in one patient due to a recurrent subcutaneous seroma. Meningitis occured in only one patient. Another rare complication was the formation of a granuloma at the catheter tip (Fig. 4). Granuloma formation may be due to reaction to the administered drugs or to the catheter tip. The thoracic region seems to predispose to this rare complication because it has the narrowest intrathecal space and a slow CSF flow. All these complications were rare particularly when compared to those of spinal cord stimulation (SCS) or shunt therapy for hydrocephalus. Due to the relatively specific spinal action of baclofen, systemic side effects are also rare. Adverse effects include: hypotonia, seizures, somnolence, nausea, vomiting, headache and urinary retention.

Conclusions

ITB is a safe and effective method for treating severe spasticity. The therapeutic dose that is required to decrease spasticity of cerebral origin is about three times higher than that required in spasticity of spinal origin. Over a follow up period exceeding 10 years, a constant baclofen dose was administered in most patients without development of tolerance. If the patients are selected carefully, ITB administration proves to be a cost effective treatment, which improves the patient's quality of life. It is indicated primarily in severe spasticity of spinal or cerebral origin that is unresponsive to oral antispastic agents and also for patients who experience intolerable CNS side effects to the orally effective baclofen dose.

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Intrathecal baclofen for the treatment of spasticity

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Summary

Spasticity is a clinical condition characterized by a velocity-dependent increase of muscle tone due to ''parapyramidal'' disturbance of the inhibitory afferents to the second motor neuron.

Intrathecal baclofen (ITB) is at present the most effective treatment for generalized spasticity provided that an accurate assessment of patients to be candidates for ITB is made. The most important patient selection criterion is lack of positive response to any oral antispastic drug or appearance of undesired side effects of such oral treatment.

Spasticity should not be treated in patients in whom it may be helpful to maintain posture due to their very poor muscle strength. When assessing a spastic patient alternative treatments such as Botox and peripheral neurotomies must also be considered, particularly in cases of predominantly focal spasticity.

According to our experience, it is advisable to divide spastic patients into two different groups: the first group including wheel-chaired and bed-ridden patients, the second group comprising spastic patients who are still able to move. In each of these two groups treatment goals vary and require different protocols for the patients' evaluation. Assessment of patients is completed with the functional index measurement (FIM) scale in order evaluate changes in patients' quality of life caused by variations in the motor performance.

Currently, treatment of spasticity with ITB is the most effective way of reducing spasticity regardless of its cause.

Keywords: Neuromodulation; wheel-chair; spasticity; baclofen; intrathecal; pump; bedridden patient; ITB.

Introduction

Spasticity is a clinical condition characterized by a velocity-dependent increase of muscle tone due to ''parapyramidal'' disturbance of the inhibitory afferents to the second motor neuron. Increase of tendon reflexes and appearance of muscle spasms are almost constantly accompanying findings.

Also, spasticity is always flanked by variable muscle weakness [1, 4, 14].

Spasticity is a clinical sign of many neurological disorders and is caused by lesions at either the cerebral or spinal level. It could be considered a positive sign of the CNS' ability to compensate for a focal or generalized loss of muscle strength, and hence spasticity should not be treated in all patients because it could be beneficial in many. Patients affected by spasticity experience variable deterioration in their quality of life mainly because of a worsening motor performance [3, 10, 24]. Intrathecal baclofen is at present the most effective treatment for diffuse spasticity [1, 3–7, 11–14]. The difference in effectiveness between oral and intrathecal administration of baclofen (ITB) is due to a significantly higher drug concentration that can be achieved in the CSF by ITB. In addition, there is a 4 to 1 gradient in drug distribution between the caudal and rostral parts of the spinal cord following ITB, thus providing for a beneficial effect at the spinal level without undesired side effects in the brain [18].

Patient selection

The most important criterion for patient selection is a negative response to oral antispastic drug treatment as this can be demonstrated by poor reduction of spasticity and appearance of undesired side effects. If spasticity must be treated but patients do not respond to any oral therapy, intrathecal baclofen is currently the most effective treatment.

However, spasticity should not be treated in patients in whom it represents a transitional phase of the disease's progression as in amyotrophic lateral sclerosis; in such cases, any treatment of spasticity will result in a reduction of muscle strength. Spasticity should also be left untreated in those patients in whom it may be helpful to maintain posture, particularly in patients with poor muscle strength.

When treating a spastic patient, alternative treatments such as botulinum toxin A (Botox^{TM}) injection and peripheral neurotomies should be considered, especially in cases of focal spasticity.

Special caution should be exercised in patients with hypersensitivity, in whom even a very small dose of baclofen may cause hypotonia and muscle weakness. If needed, additional focal treatments of residual spasticity with either Botox or peripheral neurotomies may be applied in order to improve motor performance.

In our experience, it is advisable to divide spastic patients into two groups: the first group includes wheelchaired and bed-ridden patients, the second group includes spastic patients who are still able to move.

The goals of antispastic treatment in the two groups are different. In the first group, the decrease of spasticity aims to offer better sleep, nursing and posture while in the second group, the treatment of spasticity aims to improve the patient's motor performance.

These two different targets require different protocols for the evaluation and management of patients. In both groups, clinical assessment and grading are based on the same evaluation scales i.e. Ashworth Spasticity Scale, Penn's Muscle Spasms Scale and Osteotendinous Reflex Scale. In the second group of the still-moving spastic patients, an additional computerized gait analysis is performed. Such careful evaluation of movement patterns of various muscle groups during gait is done with and without antispastic therapy in order to determine the level of required treatment.

Analysis of gait is performed using the Elite System, in which the following parameters can be recorded:

1. recruiting pattern of affected muscles during altered gait
2. temporal phase of gait
3. stance reaction forces and
4. movements of hip, knee and ankles during gait

The assessment of patients is completed with the FIM evaluation scale in order to analyse the degree of change in patients' quality of life due to variations in motor performance. The complete battery of tests described above is performed during the following stages: a) before treatment, b) during bolus test of intrathecal baclofen, c) at peak effect, and d) during long-term treatment.

Bolus test of intrathecal baclofen

The screening test of intrathecal baclofen administration is made through lumbar puncture; if necessary, the test is repeated with an increased baclofen dosage (10, 25, 50, 75 and 100 μg) at each test. The test is normally considered positive when a decrease of spasticity of about two degrees on the Ashworth Scale is achieved for at least two hours during the day of test. This common assumption is valid for wheel-chaired and bedridden patients while for walking patients the reduction of spasticity could be even less pronounced but should be accompanied by an appreciable improvement in patient's motor performance. A positive intrathecal baclofen test is a sufficient indication for the implantation of a pump.

The choice of administration device

There are two types of administration devices (pumps) that can be used for intrathecal chronic drug delivery. All systems consist of an intradural spinal catheter connected to an administration device. The administration device can be either a constant-flow gas-propelled pump or an electronically programmable pump.

In the gas-propelled pump, the solution flow is constant as it is based on the pressure of gas in the ''high-pressure'' chamber, which compresses the drug reservoir. When the drug concentration needs to be changed also dosage can be adjusted. In the electronically programmable pump, the change of daily dosage is achieved by resetting the parameters of function. Main advantage of the programmable pump is that functional parameters can easily be altered via an external programmer without any need to change the drug concentration. The pros of the constant flow pumps include low price, low weight, and smaller size. However, the relatively high cost of baclofen in Europe discourages frequent changes of daily dosages because in any such change the existing drug in the pump must be discarded and be replaced by new drug with the adjusted concentration.

Surgical procedure

In our department, implantation of an intrathecal administration pump is usually performed under local anaesthesia with exception of children and particularly non-cooperative individuals. It takes around 30 minutes without major discomfort for the patient. A large series of catheters can be used as proximal intradural catheters. They are all inserted at a low lumbar level with the tip positioned upwards, usually to the level of the first lumbar vertebra (L1). Unlike other groups, we do not think that the level of the catheter tip is crucial in extending the effect of baclofen upwards.

An extension catheter is then connected to the previously inserted intradural catheter by means of a titanium connector placed just outside the spinal processes. A catheter loop is left at that level to avoid catheter dislodgment during movements. The extension catheter is tunnelled subcutaneously to reach a pre-formed subcutaneous pocket created at the lower left abdominal quadrant. Then, the catheter is connected to the pump and the pump is placed in the subcutaneous pocket. The pump can be filled and programmed in advance. Skin sutures complete the surgical procedure. Problems connected with these systems include: catheter dislodgment, puncture or kinking, pump arrest, and incorrect programming or refilling of the pump.

In our series, only two patients presented with device-related problems: one patient suffered catheter dislocation after undergoing massage on his backbone, and the second patient, a heavily-built obese man suffering from diabetes, developed an ulcer decubitus on the skin wound overlying the pump at the subcutaneous abdominal pocket; thus the pump was replaced on the contralateral abdominal side. One should ensure that refilling of the pumps is always done in a very careful manner, because there is a substantial risk of overfilling the pump which may lead to drug overdose in the patient. It is very important to stress as a warning that with respect to ITB there are no antagonist molecules available in clinical use as antidotes. Hence, a severe syndrome of baclofen overdose must be managed in an intensive care unit. The patient is usually dismissed two days after pump implantation. Clinical evaluations are performed on a weekly basis for 3 months; thereafter the patient is evaluated at refills.

Results

A stable decrease of spasticity is observed after about 6 months of staged gradual increase in daily baclofen dose. At that point in time, the decrease in spasticity and daily dose are stabilized.

When the patient suffers exclusively from spasticity, the effects are remarkable and easily achieved in bed-ridden and wheel-chaired patients. Particularly in multiple sclerosis patients, a very low daily dose of baclofen can result in a marked decrease of spasticity. Patients who responded positively to the baclofen bolus test are expected to experience a marked and stable decrease of their spasticity irrespective of the cause. There are patients suffering from cerebral palsy in whom a decrease of spasticity seems to be only temporary; in these cases, however, an extrapyramidal component may be revealed by the decrease of spasticity [1].

In the published series, patients are usually presented as one single group and results of ITB as a diagram of progressive improvement on the Ashworth Spasticity Scale and Penn's Muscle Spasms Scale [3, 4, 8, 10–16, 19, 20, 22–24]. Several recent articles report improvement in the quality of life during long-term treatment with ITB by evaluating and scoring on the basis of quality of life (QoL) scales.

In our experience, division of spastic patients into two separate groups of: a) wheel-chaired and bed-ridden, and b) walking patients is useful in order to distinguish and elucidate the different outcomes of these two patient groups during long-term ITB.

Wheel-chaired and bed-ridden patients

During chronic ITB treatment, patients experience a stable decrease in spasticity regardless of its underlying cause, a drastic reduction of muscle spasms, improved sleep and better capacity to sit in a wheelchair, as well as easier nursing. In our experience, in order to achieve a good control of spasticity, the daily dose can be variable depending on the individual patient, the underlying disease and whether the condition has caused damage to the brain or spinal cord. In our series, daily doses varied from 25 to 1100 μg of baclofen; two different evaluations were done in both lower and upper limbs. It is important to maintain a balance between the effect on the lower and upper limbs; excessive decrease of spasticity in the lower limbs could be associated with a higher risk of decubitus ulcer, urinary retention and muscle weakness. We did not notice any variation in the distribution of the antispastic effect with respect to the different positions of catheter tip along the spine. Thus, we prefer to insert the catheter tip at level L1 or L2, avoiding its contact with the spinal cord.

Determination of the optimal daily dose depends on the individual patient's needs and the disease causing spasticity. When spasticity is due to disease affecting the brain, the required daily dose of ITB is higher than the daily dose needed to decrease spasticity in a disease affecting the spinal cord. Although variations in functional scales before and during treatment are not important in these patients, improvements in nursing, ability to sleep and maintenance of sitting position represent a marked benefit for patients' quality of life.

Patients able to walk

The effect of ITB in these patients is dependent on the cause of spasticity. When spasticity is due to acute myelitis, it is likely that patients will experience an improvement in their ability to walk provided that they follow a continuous program of motor rehabilitation. When such patients are assessed according to the FIM scale, a relevant improvement in their functional independence is observed. On the other hand, if spasticity is caused by a slowly progressive disease such as familial spastic paraplegia, the effect of ITB in terms of motor performance does not appear to be significant; however, in the long-term, when patients are slowly withdrawn from treatment, their motor performance dramatically worsens. Thus, the lack of remarkable improvement in motor performance does not indicate that ITB is useless in such patients. On the contrary, it indicates that a preservation of motor performance is achieved despite the slow progression of disease. A wide variation in daily dose may be required in order to achieve this result.

General considerations

Treatment of spasticity by ITB is presently the most effective way of reducing spasticity regardless of its cause. The best results are obtained when the right indication exists in a patient [3, 4, 8, 10–15, 19, 20, 22–24]. Any additional treatment for focal residual spasticity can initially be based on Botox and on peripheral neurotomies to optimize the results of ITB in patients with dystonic components or residual deficits of motor performance. The urological assessment of spastic patients and the appropriate rehabilitation must also be programmed in order to achieve the best results [9, 21].

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Management of spasticity in multiple sclerosis by intrathecal baclofen

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Summary

Since its introduction, chronic intrathecal baclofen (ITB) infusion has been proved to improve spasticity, spasms and related pain. In the literature, the reported clinical improvement is evident in more than 85% of the patients suffering from spasticity and in more than 66% of the patients suffering from spasms. Usually, the evaluation of spasticity is carried out by the Asworth Scale although there is not yet general accordance on the validity of this scale. It is possible that some of the scales used to assess the implanted patients are not sensitive enough to detect changes in the quality of life or functional outcome. After the pump's implantation, the overall care seems to be rather simple for a devoted team. The side effects are usually temporary but they can worry the patients. The most dangerous side effects are baclofen overdose and withdrawal syndrome. These complications are totally avoidable by adopting an approach attentive to the details regarding the patient, the device, and the procedure.

Keywords: Intrathecal baclofen; multiple sclerosis; spasticity.

Introduction

Spasticity is estimated to be present in about 60% of the patients suffering from multiple sclerosis (MS); one third of MS patients modify or discontinue daily activities as a result of spasticity [21]. Of the total population of MS patients, the potential candidates for ITB administration are about 13%. Since its introduction by Penn and Kroin in 1984 [19, 25], ITB has been proved to improve spasticity, spasms and related pain. There are more than 30 series [2, 3, 5, 20] on spasticity treated by ITB with a total of more than 300 patients with MS reported. The mean follow-up varies but usually it does not exceed a 2–3 years period; recently, a study with a follow-up of more than 5 years was published [25]. In general, there is accordance in the positive results in the various studies. In the literature, the percentage of patients who have improved after ITB exceeds the 85% with regards to spasticity and the 66% with regards to spasms. Improvement in pain has also been reported. The indications for ITB include: a) chronic diffuse spasticity (more severe than grade 3 of the Ashworth Scale), which is either unresponsive to oral antispasmodic drugs or the treatment has unacceptable adverse effects, and b) a positive response to the ITB screening test. In MS patients, it is advisable to implant a pump with an accessory port in order to perform more easily examinations of the cerebrospinal fluid (CSF) for the study of the disease.

Postoperative management

In spite of the good clinical results of ITB on spasticity, clinical studies focused only on its effect on MS patients are limited. The stage and the course of the disease are not described in many of the studies. This is important as the drug dose could vary in relationship to the neurological condition. It is important to know if the decrease in spastic symptoms after ITB infusion is due to the long-term intrathecal infusion or to a change in the course of MS [7]. On the other hand, it is equally important to know if an increase of spasticity could be due to either drug tolerance or deterioration of MS.

After implantation, the management of patients undergoing ITB treatment appears to be rather simple for a devoted team; it should be kept in mind, however, that the patient must be followed-up regularly and carefully. Usually, the evaluation of spasticity is carried out by the Asworth Scale (AS), although there is not yet general accordance on its validity [17]; notably, the AS is not sensitive enough for detection of small changes in moderate or severe spasticity and, consequently it may not be

very useful in evaluating the functional consequences or the dynamic aspects of spasticity [15]. In the evaluation of spasticity, the soleus stretch reflex could be useful in patients with MS [15] as well as other scales [8] including the Tardieu scale [24]; the latter takes into consideration the velocity-dependent nature of spasticity. Since spasticity may co-exist with other motor disorders it is not easy to distinguish it clearly. This problem is particularly important in walking patients. Several dose adjustments, over a period of a few weeks to a few months, may be needed in order to achieve the maximum clinical effect. The programmability of the pumps allows fine adjustments, which can resolve noctural spasms with a higher dose at night or allow the increase of spasticity during the day for the performance of particular tasks. Recently, new pumps offer to the patients the options of partial control over the pump programming itself and of bolus administration of the drug when required, a development that clearly improves the flexibility of the device.

The importance of physical therapy cannot be underestimated. The efforts to restore the appropriate cooperation of agonist and antagonist muscles should be maximized and, if necessary, re-evaluation of the orthosis and sitting systems should be undertaken. The goals of ITB include functional improvement and improvement in the quality of life (QOL). In the literature, the data are not so clear on these issues. In long-term evaluations, it seems that there is no improvement in disability or perceived health status [25], while in evaluations using the Sickness Impact Profile (SIP) [14] a statistically significant improvement was documented; furthermore, a significant improvement was demonstrated when the Barthel Index Score (BIS) was used [2]. It is possible that certain of the assessment scales were not appropriate for detecting changes particularly in the QOL or functional outcome. Moreover, patients with MS can have cognitive dysfunctions compromising the correct execution of the tests. In the absence of a ''tailored'' scale, the functional benefits in tetraplegic patients may be underestimated [2]. A new method of evaluation, particularly in MS patients should be developed. Notably, ITB was associated with a much higher satisfaction rate among patients compared to the oral treatment [21].

Management of side effects and complications

The side effects are mainly pharmacological whereas the complications can be either pharmacological or surgical. The management of urinary dysfunction is an aspect of this therapy that should be done in a very careful manner. Decrease of detrursor hypertonia and hyperactivity has been reported in 50% of the patients [13]; the possibility to exacerbate existing urinary incontinence or retention has not been yet clearly addressed in the literature. Incontinence occurred in two of our patients and was associated with reduction of patient's satisfaction for the good result of ITB on spasticity. Any potential impact of ITB on erection and ejaculation [6] is usually reversible and not a sufficient reason for interruption of this treatment; nevertheless, this is a very important issue in patients with partial spinal cord damage and should be addressed because the patient experiences this impairment as an additional deficit and evidence of further progression of the disease. Furthermore, the impairment of intestinal functions [16] and problems such as constipation should be expected but they are usually treated with specific drugs. Usually, adverse effects such as drowsiness, dizziness, and slurred speech are transient and require only lowering of the drug dose [18]: with diligent follow-up, these problems can be solved easily. Yet, one should be aware of the possibility that these findings could represent a worsening of MS when they appear several months after the onset of therapy. The phenomenon of tolerance to baclofen is manifested by a gradual increase of the dose required to produce a previously obtained positive effect or by the gradual decrease of the effect produced by a given dose [1]. The first manifestation of this phenomenon appears in about 15–20% of the patients, usually within the first 12 months after implantation. The adjustment of baclofen dose usually resolves the problem. The second manifestation of this phenomenon is reported in 3.5–15% of the cases, without being more common in MS [5], and can be associated with pruritus or paresthesias; usually, a ''drug holiday'' is required to restore the clinical benefits. The cause is thought to be related to a decrease of $GABA_B$ receptors after repeated drug infusion; recently, however, it has been observed that there are no significant alterations in $GABA_B$ receptor binding sites [11]. During a ''drug holiday'', intrathecal morphine is usually administered for 1–2 months; in certain cases, however, the morphine treatment may become necessary for a very long time. Notably, morphine can also cause side effects such as vomiting, somnolence or constipation.

Another issue is the possible decrease or termination of the infused dose because this is no longer required; it is not clear why and when this can occur and if it occurs mainly in MS patients. It has been postulated that this

could result from functional or structural changes at the spinal level induced by the prolonged effect of highly concentrated baclofen [7]. In our series, this phenomenon was noticed in 12% of the MS patients. We observed a similar phenomenon in two patients with supraspinal spasticity (unpublished data) and certainly, this requires further studies. The most important pharmacological complication that must be avoided is baclofen overdose; it is usually due to human error in pump programming or pump refill. Its incidence varies between 0 and 5% [5]. The symptoms include hyporeflexia, severe hypotonia, sedation or coma, and respiratory depression; for the most part, these are reversible without permanent damage. The errors of the programmer leading to these complications are totally avoidable if one is attentive to details. If overdose does occur, the airways, breathing, and circulation must be secured and maintained. The pump must be stopped and the baclofen removed from the reservoir; physostigmine should be administered intravenously and a lumbar puncture should be done to evacuate CSF in order to reduce the drug concentration in it. Antiepileptic drugs may be helpful in treating or preventing seizures related to overdose. The most dangerous potential complication of chronic intrathecal infusion is withdrawal. Due to a failure of the infusion system or to an empty pump, this problem is usually manifested with a recurrence of the patient's baseline spasticity; yet, in few reported cases, the withdrawal caused fever, seizures, unstable blood pressure, and deterioration of consciousness: if not treated promptly, this could progress over 24–72 hours to renal and hepatic failures, disseminated intravascular coagulation, and death. In the literature, the withdrawal syndrome was observed mostly in cervical spinal cord injury patients but MS patients can also be affected [5]. The therapy aims to restore urgently the ITB infusion by refilling the empty reservoir or correcting the damage in the infusion system. In addition, the appropriate drugs should be offered to treat fever, seizures or renal failure. The withdrawal syndrome can also occur 1–7 days before the drug's residual volume reaches the volume of alarm (usually of 2.0 ml): in these cases, the syndrome does not develop if the alarm volume is increased to 4 ml [23]. Our current improved understanding of this syndrome and its urgent treatment obliges us to program carefully the pump refills for each patient.

In the literature, the reported cases of epilepsy in patients with chronic ITB are rare, although a relatively higher incidence of epileptic seizures in MS patients undergoing ITB has been reported [22]. In these series, the onset of epileptic seizures was associated with aggravating factors such as febrile illness or baclofen overdose. In the severe MS patients, cognitive abilities are reduced, so, it is important to study if and when there is impairment of these functions by the long term ITB. Notably, low doses of baclofen have improved memory performance while higher doses have impaired it [12]. It would be useful to know the baclofen dosage that can cause memory deficits and this should be specified. In further research, particularly in non-ambulatory patients, it is advisable to adjust caloric intake once spasticity is reduced because the caloric requirement in patients with good spasticity control is reduced [10]. During follow-up, in patients with potential renal insufficiency, a check of renal functions should be performed. General anaesthesia could cause adverse effects because of interactions of baclofen with the anaesthetic drugs; special care should be taken for this possibility in the perioperative period [9]. The pump infusion could be discontinued; however, if this is extended there is a risk of withdrawal syndrome. The surgical complications are rather frequent affecting up to $1/3$ of patients [20]; the most common complications are system failure, CSF fistula, and infections. The main cause of technical failure of the system is damage in the spinal catheter (about 50%). The catheter damage includes dislodgments, migration, kinks, obstructions or disconnections from the pump. Recently, the introduction of improved catheters made this complication more rare. The formation of granuloma on the spinal catheter tip is very rare in patients with ITB compared to morphine infusion; however, this should be suspected in patients with rapid weakness of the lower limbs. Infection of the pump is rare and usually related to the procedure of surgical implantation; the periodic refills of the pump or other concurrent infections (respiratory, urinary tract and skin decubitus) do not seem to be a risk factor for contamination of the pump [4]. Nevertheless, careful skin disinfection is mandatory during refills.

In conclusion, ITB is a useful therapy with good clinical results. In the future, in order to improve the application of this therapy, we should do studies with prolonged follow-up periods, develop better systems for evaluation of spasticity, and record carefully the types and occurrence of pharmacological and surgical complications as well as the interactions of baclofen with other drugs. In order to eliminate avoidable complications, this type of therapy should be restricted to specialized centres.

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Surgical management of spasticity of cerebral origin in children

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Summary

In children, spasticity is commonly seen in the context of cerebral palsy (CP), but also following head injury, cerebral infarct or other brain insults. CP is a wide term used to describe a constellation of symptoms that characterise the physical impairment of movement due to abnormal brain development. The management of spasticity is tailored according to the clinical picture of the child. Ambulatory mild spastic diplegics tend to reach the maximum of their disability in the first few years of life, and change little after the age of 5–7 years. Such patients who are seen between 3–5 years and who attempt to mobilise with walking frames are often good candidates for either dorsal rhizotomy or intrathecal baclofen (ITB) administration with the implantation of an indwelling pump. Non-ambulatory mild spastic diplegics and spastic quadriplegics have more profound spasticity, painful spasms, orthopaedic deformities, and difficulties with daily care and posture. ITB has become established as the first line of surgical treatment for these patients. In the last decade, there has been a definite trend away from ablative treatments and towards reversible stimulation and infusion systems. Current pumps have practical limitations but, in the next decade, it is anticipated that technological improvements will render the pumps more patient friendly.

Keywords: Neuromodulation; spasticity; children; cerebral palsy; baclofen; pump; ITB.

Cerebral palsy – spasticity

Spasticity is a movement disorder defined as the velocity-dependent hyperactivity of the tonic stretch reflexes that control muscle tone. In simpler terms, when examining a joint, whereas normally there is equal distribution of resistance (tone) throughout the passive movement of the joint, in spasticity the more the joint moves the higher the resistance (tone) throughout the passive movement of the joint.

Despite significant progress in management, there is still considerable confusion and poor understanding of spasticity, because it is not a clear disease entity, but encompasses several inter-related motor disorders. In children, commonly spasticity is seen in the context of cerebral palsy, but can been seen also following head injury, cerebral infarct or other insult that leads to supratentorial damage. As the same pathophysiological and management principles apply, most discussion will centre on cerebral palsy. Spasticity can result following spinal cord injury, such as spinal trauma. This is rare in children, but commoner in adults, and will be dealt with elsewhere in this book.

Cerebral palsy (CP) is a wide descriptive term, admittedly not with a clear definition, used to describe a constellation of symptoms that characterise the physical impairment of movement, due to abnormal brain development. Under this wide term, complex movement disorders are included such as spasticity, athetosis, ataxia and dystonia. Recently, an attempt was made to define better the term cerebral palsy, as so far it had been used loosely. An International Workshop on Definition and Classification of Cerebral Palsy was held in Bethesda, Maryland in July 2004. As a result, Cerebral Palsy was defined as "a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception and/or behaviour, and/or by a seizure disorder" [10].

Commonly, a patient affected by cerebral palsy has a predominant component of the movement disorders, but very frequently also a combination of all other types as well. So in effect, the division to spastic, athetotic, ataxic or dystonic cerebral palsy is characterised according to the predominant symptom. Significant influence on the management of these children plays the level of intellectual and educational development. Some children are intellectually normal or near-normal and can follow

mainstream school despite their physical disabilities and others are severely affected intellectually, which further compounds their clinical management.

Cerebral Palsy is usually the result of an insult to brain development early in life. In full term babies, a common event is a perinatal hypoxic episode. In premature babies, several risk factors have been identified predisposing to cerebral palsy such as the presence of ductus arteriosus, perinatal hypotension, requirement of blood transfusion, need for prolonged ventilation, pneumothorax, sepsis, hyponatraemia, need for total parenteral nutrition, seizures, intraventricular haemorrhage and brain parenchymal damage and ventricular dilatation [36]. Among babies born weighing less than 1500 g, the rate of cerebral palsy is 70 times higher compared to those weighing 2500 g or more at birth [26]. Children who suffered a distinct cerebral insult, such as infraction or haemorrhage will have evidence of such abnormality on imaging. The majority of children with cerebral palsy have suffered a perinatal hypoxic insult, severe enough to impair basal ganglia function, which are nevertheless structurally intact; so these children have normal brain structure on imaging, but can be profoundly disabled by their condition.

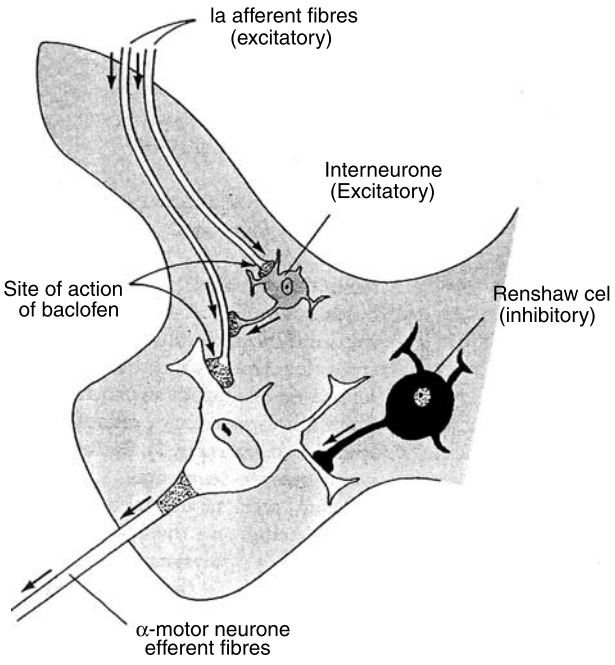

Fig. 1. Diagrammatic representation of the mechanisms implicated in spasticity and site of action of baclofen (Adapted from McLean [34])

Pathophysiology

Understanding of the underlying pathophysiological mechanisms of spasticity is important for the design of effective treatment strategies. In its most simplistic and elementary interpretation, the basis of spasticity is a hyperactive stretch (tendon) reflex. Obviously, it is a complex movement disorder with several underlying pathophysiological mechanisms in action at any given time. The previously believed mechanism of fusimotor hyperactivity has fallen out of favour. It was believed that increased tendon reflexes were due to hyperactive gamma efferent activity on the basis of which the surgical treatment of selective rhizotomy evolved in the late 1970s and early 1980s. Subsequent studies though showed that there is no evidence of increased muscle sensitivity or increased Ia discharge in response to muscle stretch [49].

The main mechanism predominantly operative in spasticity is considered to be excessive excitation due to deficient supratentorial inhibition from descending brain pathways. In response to any muscle movement, the muscle spindles produce normal afferent input. Normally, at the level of the spinal cord, there is presynaptic inhibition of Ia terminals. This presynaptic inhibition is due to gamma amino butyric acid (GABA) released from inhibitory interneurons, which interact with receptors on the Ia terminals (Fig. 1) [49]. In addition, near the GABA receptors are also receptors for benzodiazepines such as diazepam, which have similar effect. These inhibitory interneurons are modulated by descending neurons that come from the basal ganglia and travel down the spinal cord. A lesion that reduces this presynaptic inhibition, leads to overdrive of the stretch reflex circuit due to diminished presynaptic inhibition. The result of reduced presynaptic inhibition is relative excess of excitatory neurotransmitters such as glutamate and aspartate. Methods that could enhance this diminished presynaptic inhibition could improve spasticity in theory. Other mechanisms involved are reduced Golgi tendon organ inhibition, reduced Group II myelinated fibres inhibition and reduced recurrent Renshaw cells inhibition at the anterior horns of the spinal cord [49]. In addition to the pathological enhancement of the stretch reflexes, there is also pathological overlap between agonist and antagonist function [37].

A direct consequence of the long standing increase of the muscle tone is the development of *joint contractures*. Contracture is defined as the persistent loss of full passive range of motion in a joint due to permanent structural soft tissue changes. While permanent contractures can be caused by a variety of reasons, in the context of spasticity, the increased tone usually leads to contractions

of the flexor muscles in the arms and extensor muscles in the legs. Prolonged muscle contractions eventually lead to contractures in the joints that these muscles control. The cause of these contractures is not entirely clear. It may be due to muscle fibrosis or change of muscle fibre type complement, which leads to muscle shortening, or due to change in dynamic properties of the muscles, which develop lower sensitivity threshold. Of interest is that such contractures are seen to a lesser degree in adult patients who develop spasticity as result of stroke or other brain injury.

Epidemiology

For every 1000 live births, 1.5–5 children will sustain birth injury which will lead to cerebral palsy [2, 26]. At least 50% of them will develop spastic cerebral palsy and another 25% will manifest some mixed form of athetotic-ataxic-dystonic cerebral palsy with obvious spastic component. Almost all of these children will require treatment for their spasticity and the coexisting orthopaedic problems. One in five children with CP have severe intellectual deficit and are unable to walk. Cerebral Palsy carries a 1% mortality per year in the first five years of life, declining to 0.35% per year up to the third and fourth decade of life [12]. Deaths are rare after the age of 25 years. Severe motor impairment is associated with increased mortality [12]. Children born after more than 32 weeks' gestation are at risk of significantly higher mortality than very preterm infants, largely due to the higher rates of intellectual disability [12].

Clinical manifestations of spasticity

Commonly, the clinical manifestations are not seen in the first few months of life, but are appreciated as the child develops in the first two years and fails to ''hit'' his normal developmental milestones. As the child begins to grow, neuromuscular development is lagging behind and the features of spasticity are gradually appearing.

Three distinct clinical syndromes are recognised, although intermediate pictures are not uncommon: *i.* Premature children born before 32 weeks gestation who suffered any degree of encephalopathy develop spastic diplegia, with the lower limbs more affected than the upper limbs. *ii.* Children born at term who suffered a perinatal hypoxic event resulting in encephalopathy develop spastic quadriplegia, with all four limbs similarly affected. This picture is observed and in other acquired forms of cerebral palsy (e.g. following head injury, survival from drowning or cardiac arrest etc). *iii.* Children who develop neonatal intraventricular haemorrhage, usually Grade IV with significant parenchymal damage in the region of the basal ganglia develop spastic hemiplegia that affects arm and leg on one side.

A minority of children with spastic diplegia can walk independently, with variable degrees of help. The majority of children with spastic diplegia and almost all with spastic quadriplegia are wheel chair bound and typically suffer painful flexor spasms of variable degree, which interfere with almost all activities of daily living. They may have difficulty in sitting in the wheel chair or even lying down from painful spasms of the trunk muscles, as well as have painful spasms of their limbs. As a consequence of this, there is variable degree of muscle weakness, easy fatigability and loss of dexterity, which in severely affected children can interfere with feeding, dressing, toileting and other basic life activities. In mixed types of cerebral palsy, there is variable combination of ataxia, athetosis and dystonia, which can complicate assessment and choice of treatment even more.

Examination of the limbs shows invariably increased tendon reflexes and clonus. In the early 1960s, Ashworth devised a simple scale to classify the degree of raised tone, ranging from 0–4 [8] (Table 1). While over simplistic, it is still used today as it provides a coarse standard for comparison. In the 1980s, this scale was modified to extend from 0–5 [13]. Like all clinical scales, in both original and modified forms, it provides only a broad

Table 1. *Ashworth scale*

Score orig/mod	Original scale [8]	Modified scale [13]
0/0	no increase in tone	no increase in tone
1/1	slight increase in tone, catch when limb is moved	slight increase in tone, catch and release when limb is moved
1/2		slight increase in tone, catch when limb is moved followed by a minimal resistance throughout the remaining movement
2/3	more marked increase in tone but limb is easily moved	more marked increase in tone but limb is easily moved
3/4	considerable increase in tone, passive movement difficult	considerable increase in tone, passive movement difficult
4/5	limb rigid in flexion or extension	limb rigid in flexion or extension

measure of the degree of tone increase, and by no means describes the complex movement disorder and clinical picture that almost all patients have [38]. Nevertheless, like all simple scales, it has stood the test of time and is still in use today.

Most patients with long standing spastic quadriplegia have a variable degree of limitation of joint range of movement due to contractures. During clinical assessment it is often difficult to establish to what extent the limitation of range of movement is due to the muscle contractions or due to fixed contractures. Often, the only way to differentiate is examination under anaesthetic, while the child is asleep for another procedure (e.g. baclofen trial lumbar catheter insertion).

Clinical assessment and management of children with spastic cerebral palsy requires multi-disciplinary team approach, with active involvement of neurosurgeon, orthopaedic surgeon, rehabilitation physician-physiatrist and physiotherapist. In addition to assessment of tone, movement pattern, and joint contractures, a thorough assessment of functional performance is required. Several scoring systems are used, the Wee Functional Independence Measure (FIM), the Gross Motor Function Classification System (GMFCS) and the Gross Motor Function Measure (GMFM) being the more popular ones.

Natural history of spasticity in cerebral palsy

Children with spastic diplegia tend to reach the maximum of their disability in the first few years of life, and change little after the age of 5–7 years. The ones affected in a milder degree usually do not deteriorate with time at all. As most of them are intellectually intact, they often manage to follow mainstream school with help in their physical disability. More severely affected children can experience deterioration of symptoms in their legs with time. They also suffer from a variable degree of intellectual impairment, which requires appropriate educational support. Overall, up to a third of patients with CP complete education beyond secondary school and 5% pursue higher studies. A third of them are employed in mainstream jobs [35]. The intellectual impairment is the major determinant of social integration [35]. Children with spastic quadriplegia continue to deteriorate throughout their life, and usually by the age of 10 years they have already significant problems of day-to-day care. While most of these patients are of thin build, as they grow to become young adults and their body mass increases, it becomes very difficult to care for them.

Patient management

Management of children with spastic cerebral palsy is multi-faceted and aims to address as many of their problems as possible: constraint mobility, spasticity, pain, posture, joint contractures, quality of life. While isolated management of spasticity can offer symptomatic improvement, these difficult patients can benefit from the maximum of what can be achieved only in the context of a multi-disciplinary team, with significant additional input from orthotists, physiotherapists and community physicians.

Management of contractures – orthopaedic treatment (tenotomies, tendon transfers, rotation osteotomies)

While beyond the scope of this chapter, orthopaedic surgeons involved in management of patients with spastic cerebral palsy have a proactive approach to management of contractures, aiming mostly to prevent them. Severely affected spastic quadriplegics with contracture deformities, can benefit by Botulinum toxin A injections in selected muscles groups, tenotomies (e.g. adductor tenotomy in the hip, hamstring lengthening for the knee), muscle release, tendon release, tendon transfers or even derotation osteotomies (usually of the femur) to modify the vectors of action of different muscles and improve function [11]. As the mature gait pattern develops by the age of 7 years, orthopaedic surgery should be avoided in ambulant children before that age [42]. Derotation osteotomies usually are not undertaken before the age of 8 years, due to high recurrence rate [42]. With the advent of less invasive treatments such as intrathecal baclofen, the need for such treatments is decreasing [22].

Posture-orthosis

Wheel chair bound patients have ever increasing demands for orthotic aids to facilitate their sitting and posture. Most patients with severe long standing spastic quadriplegia have abnormal truncal posture and require regular modifications to the wheel chairs to provide comfort. This often proves a major challenge.

Management of spasticity and pain

Control of spasticity usually leads to reduction of pain from spasms. Management of spasticity depends on the clinical condition of the patient when first seen, the severity and type of movement disorder and the age. Prior to embarking on any treatment of children with spasticity,

it is important to have long discussions with the family and other carers to establish common ground of expectations from the treatment. As in most cases any treatment can offer only a moderate alleviation of symptoms; unrealistic expectations from the family result in failure and breach of trust.

Commonly, in the early stages spasticity is managed medically with some of the agents described below. In most cases, the effect of medical therapy is at best mild and is attenuated after the first few months or a year. After that, while medical treatment can continue, it is largely ineffective, and surgical options are explored. A management scheme of the different clinical forms of spasticity is outlined, followed by more detailed discussion of the different options.

Management of ambulatory mild spastic diplegics

Provided that these patients are seen early, in the first few years of life, there is great scope for maximising their potential and some of them may even walk unaided or with minor help. Commonly, medical treatment is tried initially but its effect is not dramatic. As the severity of the disease progresses, the patient moves to percutaneous Botulinum toxin A injections and to more invasive surgical treatment. As this group tend to have more mild movement disorder, early surgical treatment offers the best long term returns.

Medical management. From the various pharmacological agents discussed in detail later, only oral diazepam and baclofen have a proven effect on spasticity and pain but have dose-related side effects, making long-term administration problematic. They are usually tried for limited periods in this group of patients. Botulinum toxin A injection to selected muscles can improve spasticity. Its effect lasts for 3–4 months and can only be repeated a few times. So this treatment is good for a limited period of time of a few months up to a year.

Surgical management. Selective neurectomy or neurolysis by alcohol or phenol injection has been utilised in the past to reduce the activity of muscles which are perceived to be overactive. Usually it is not appropriate for this group of patients, and in any case, it has fallen out of favour in recent years, as the trend for reversible treatment modalities has taken pace.

Patients who are seen early in life, between 3–5 years, who attempt to mobilise with walking frames, are often good candidates for ablative procedures such as the different variants of dorsal rhizotomy. Dorsal rhizotomy has been evolving for over 4 decades and when performed judiciously it can improve walking pattern of these patients, without other significant complications. While these patients are of thin build when they are young, they increase their weight following successful rhizotomy and later on in life their mobility can regress. As with all surgical treatments of spasticity, after surgery, any pre-existing weakness is unmasked and most patients require intensive physiotherapy in the first few postoperative months, to capitalise on the beneficial effect of the treatment. Recently, intrathecal baclofen has been tried in this group of patients with success.

Management of non-ambulatory mild spastic diplegics and spastic quadriplegics

These children are commonly more severely affected in all respects, with more profound spasticity, painful spasms and all the other problems with orthopaedic deformities, difficulties with daily care and posture. In addition to spasticity, most patients have an element of ataxia, athetosis and dystonia. Most patients deteriorate over time and eventually become candidates for surgical treatment. Patients with acquired spasticity secondary to brain injury of various causes behave in a similar way to children with congenital spastic quadriplegia and are managed in a similar way.

Medical management. Oral diazepam and baclofen are commonly administered in the early phases of management, with moderate success. The effect of these agents eventually becomes blunted and while the dose is gradually increased to improve the clinical response, the side effects after a point prohibit further use and force discontinuation.

Surgical management. Selective dorsal rhizotomy can improve spasticity in lower limbs, but usually the results are limited as these patients tend to be severely affected. Intrathecal baclofen (ITB) has shown promising short and medium term results and has become established as the first line of surgical treatment for these patients.

Medical management of spasticity

For most patients, success of medical management involves trial and error as variable responses have been demonstrated to different agents, and some patients develop significant side effects without enjoying any benefit.

Diazepam

Diazepam is a benzodiazepine and enhances presynaptic inhibition at the spinal cord by potentiating the effect of gamma-aminobutiric acid (GABA) [48]. In addition, it has a tranquilizing, sedative and anticonvulsant effect,

which contributes to the overall action on patients with spastic cerebral palsy, especially those with high levels of anxiety. It has a good effect in reducing spasticity and pain associated with spasms, although its effect on flexor spasms is not as good as that of baclofen. Its main limitation is the dose related drowsiness, somnolence, vertigo and dizziness. Physical dependence is well described and should be borne in mind when prescribed in patients for long periods.

Dantrolene

Oral dantrolene sodium has been shown in double blind trials to decrease spasticity and all its manifestations in more than half of the children with cerebral palsy that were treated with it [44]. While it decreases spasticity in some patients, it may not influence the level of pain associated with the spasms. Significant side effects are seen in some patients such as irritability, lethargy, drowsiness and exacerbation of pre-existing seizures. Increase of liver enzymes has been reported in children. For this reason, long term dantrolene administration in children requires careful follow up.

Clonidine

Oral clonidine has been shown in clinical trials to decrease spasticity in half of the patients treated with it [44]. A significant number of patients develop complications such as postural hypotension, lethargy, dizziness, drowsiness and insomnia, without experiencing any reduction of tone. Side effects are dose related. Relief of pain associated to the spasms is variable. Its effect in children is debatable.

Tizanidine

Oral tizanadine has been shown in clinical trials to improve spasticity. It has been compared to oral diazepam and baclofen and has been found to provide better symptomatic relief. Over 80% of patients show some improvement of spasticity. Side effects are seen in more than half of the patients and include somnolence (the commonest), dizziness, weakness, fatigue and sleep disturbance. While in adults these are not severe enough to require withdrawal of the medication in children the rate and intensity of complications is higher and makes it unsuitable in most cases [44].

Gabapentin

Oral gabapentin has been shown in double blind controlled trials to reduce significantly spasticity and pain in adults but its effect in children has not fully explored. It may prove promising.

Baclofen

Baclofen is a GABA agonist with multiple actions within the central nervous system. Its action relevant to spasticity is that of a pre-synaptic inhibition of release of excitatory neurotransmitters (glutamate, aspartate), mediated via the GABA-B receptors situated in Rexed laminae II & III of the spinal cord [3, 40, 48] (Fig. 1). This in part substitutes for the lack of inhibitory control from the descending pathways. Baclofen decreases stiffness and increases the threshold of the stretch reflex [37] but also improves spasticity by increasing selective activation, and hence possibly counteracting co-contraction [28]. In successful cases, baclofen induces a reduction of stiffness by 30%, reduction of the stretch reflex amplitude by 35% and increase in the threshold of the stretch reflex by 100% [37]. From clinical practice it is known that there is a rather narrow window of baclofen concentration, which offers reduction of spasticity without causing global muscle weakness. Indeed, a common method of determining the optimal daily dose of baclofen that the intrathecal pump delivers, is to increase the dose high enough to cause unwanted global weakness, and subsequently reduce the dose to the maximal desirable effect.

Oral baclofen has been shown in double-blind controlled trials to reduce spasticity in children with cerebral palsy. Its effect on pain is debatable. Approximately, a third of the patients develop significant side effects such as somnolence and hypotonia, which forces discontinuation of the medication. Side effects are dose related. Oral administration does not achieve good concentration in CSF, as gastrointenstinal absorption becomes prolonged with higher doses [48]. For this reason, direct intrathecal delivery has been employed for the last fifteen years, with proven satisfactory clinical effect [3, 4, 6, 18, 22, 23, 29, 30, 32, 52]. In patients with spasticity when an attempt to move a joint is initiated, the agonist muscles are activated first but within a very short period of time, the antagonist muscles begin to activate as well, opposing strongly the action of the agonists, and thus creating the clinical picture of spasticity. As Electro-Myo-Graphy (EMG) studies have shown, intrathecal baclofen breaks down that simultaneous muscle activation, allowing selective activation of the agonists first, while the antagonists remain dormant, in a pattern similar to that seen in normal individuals (Fig. 2) [17, 45]. It improves the temporal

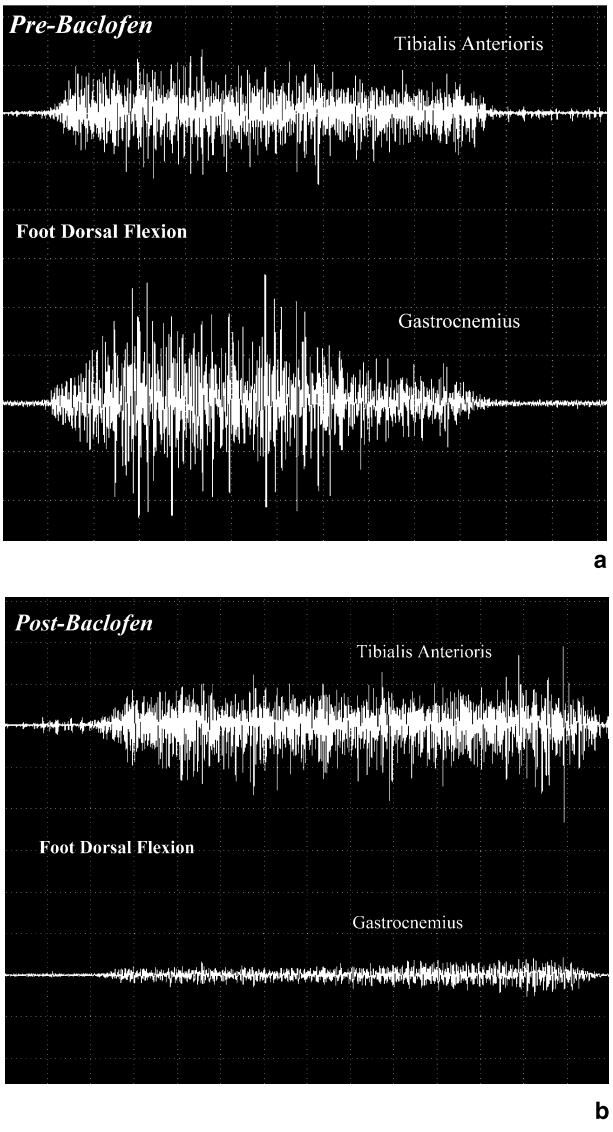

Fig. 2. Representative example of the effect of intrathecal baclofen on foot dorsal flexion. (a) Before baclofen administration. Both agonist (tibialis anterior) and antagonist (gastrocnemius) muscles fire almost simultaneously, resulting in spasticity. (b) After baclofen administration the agonist muscle (tibialis anterior) is firing unopposed, in a manner similar to normal, corresponding in a clinical improvement of spasticity. (in all recordings amplitude is 200 μV/div and time is 20 msec/div)

pattern of muscle activation establishing a more physiological sequence [45].

Botulinum toxin A

Botulinum toxin A (Botox/Dysport) is a locally acting antispasmodic exotoxin which, when injected in to a muscle, blocks its neuromuscular junctions and consequently the muscle becomes paralysed for the duration of the action of the drug. Administered in carefully selected muscle groups, it can improve spasticity, and by result, motor function and passive range of movement. In double-blind controlled trials it has been shown to produce significant reduction of spasticity and improvement in range of joint movement [9]. It is particularly effective in alleviating pain associated with spasms. It carries a small incidence (5%) of tolerable complications such as pain or weakness at the injection site. The downside for this easily administered treatment is that its effect lasts only 3–4 months, and after a few administrations it becomes less pronounced so the treatment becomes ineffective. So this treatment is good for a limited period of time of a few months up to a year and cannot offer any long term improvement [44]. It is often used in association to adductor-release surgery in the early postoperative period, or in conjunction with casting, during the period of its action. Its effect is directly related to the experience of the doctor administering it, as careful selection of muscles for injection is important.

Surgical management of spasticity

As in other branches of neurosurgery, surgical management of patients with spasticity has been influenced by trends and technology. In the 1960s, 70s and early 80s, ablative surgery in the form of rhizotomy or DREZotomy were widely used. Since the 1990s, as the technology or indwelling pump infusion systems has improved, there has been a significant shift towards pump implantations for direct infusion of Baclofen in the CSF. Both surgical approaches have pros and cons and different indications. Admittedly, the use of sensory rhizotomy demands considerable specialised expertise from the surgeon as well as significant intraoperative neurophysiological support, and for this reason it had not been widely established even in its heyday, and has gradually been restricted to spasticity centres with long expertise on the technique. The recent advent of indwelling pump implantation for baclofen infusion technically is not particularly demanding as it represents an extension of widely used neurosurgical techniques (e.g. insertion of lumbar shunts) and for this reason it has been received well by neurosurgeons who did not necessarily have long experience in the surgical management of spasticity.

Neurotomies, neurectomies

With the advent of other less destructive procedures, neurotomies have fallen out of favour. Nevertheless, in

patients with severe spastic quadriplegia and significant hip adductor spasticity, obturator neurotomy can improve the situation. In the past, complete obturator neurectomies were performed and they proved to result in uncontrolled hip abduction contracture due to complete loss of opposing adduction. For this reason complete neurectomy was superceded by selective partial neurectomy of the anterior branch of the obturator nerve, with good reported results in up to 80% of the patients [53].

Dorsal (posterior) rhizotomy

Sensory posterior-dorsal rhizotomy was used in the late 19th Century in the treatment of spasticity. In its current form, it has been evolving since the 1960s and its proponents advocate good results following its correct and judicious use. The original idea that has evolved and was established by Gros was to divide sensory incoming fibres at the level of the dorsal root of the spinal cord, based on the pattern of muscle involvement observed preoperatively [41]. The idea was to preserve what they called ''useful'' spasticity, which helps limbs and trunk to function (stand, walk etc) and abolish ''harmful'' spasticity, which impedes normal movement by creating tone imbalances. To achieve this, through a lumbar laminectomy or laminotomy, intraoperative stimulation of rootlets was performed at the segments of L2-S1 and electromyography and muscle palpation was used to monitor the result, and taylor the lesion accordingly. Variable results have been reported, depending on the indications for surgery, with success varying from 50% for hip adduction, 68% for improvement of ambulation, 75% for prevention of orthopaedic complications and 100% for improvement of sitting ability [2].

A major advance in the concept of dorsal rhizotomy came from the work of Sindou, who was a student of Gros. In his university thesis, he described that as the sensory rootlets approach the Dorsal Root Entry Zone (DREZ) in the spinal cord, they assume characteristic positions within the rootlet. The larger lemniscal fibres take a central position within the rootlet, whereas the type Ia myotatic fibres line lateral to them. He described the technique of *DREZotomy*, in which you can divide the nociceptive fibres as they left the rootlet to curve towards Lissauer's tract, by placing an incision into the spinal cord at the DREZ, in patients with chronic pain. Subsequently he described a modification of this technique for the surgical treatment of spasticity. By extending the cut at DREZ deeper, the Ia fibres can be severed as they travel towards the dorsal horn of the spinal cord. These lesions can be performed at the ventral side of the entering sensory rootlet, to ensure preservation of the larger lemniscal fibres which enter more laterally [46]. DREZotomy has been used predominantly for painful spasticity affecting useless limbs, without aiming to improve function with a claimed 75% success rate of improvement of symptoms and a 10% improvement of motor function. Sindou's technique was later modified by Fraoli and Guidoti [21].

Further modification of dorsal rhizotomy came in 1976 from Fasano, who devised a *functional selective posterior rhizotomy* [20], which is widely practiced today. Following stimulation, he demonstrated the presence of abnormal response and/or diffusion of muscle response to areas outside the myotome of the stimulated nerve. Fasano originally applied the technique by stimulating the sensory rootlets at the spinal cord level. Peacock later improved the technique by applying the stimulation and lesion to the cauda equina, in order to avoid the transient urological dysfunction that has been observed when lesioning is performed at the spinal cord level [39]. To avoid urological complications, lesioning of S2 rootlets should be avoided [27]. In practice, following laminectomy or laminotomy and exposure of the rootless of the cauda equina, intraoperative stimulation is performed and responses are recorded with electromyography and clinical observation of muscle contraction. The rootlets, the stimulation of which produces abnormal response beyond the expected myotome, are divided. Care is taken to monitor the bulbocavernosus-clitoris reflex. Most authors have described good overall result in 75% of patients, a trend towards less lesioning, satisfactory reduction of spasticity, good improvement rate of walking range in ambulatory patients, some improvement of motor function in non-ambulatory patients, small incidence of intraoperative complications such as bronchospasm and aspiration pneumonia, small incidence of postoperative CSF leak, small incidence of lumbar instability as result of the laminotomy (less than 10%) and small incidence of urological dysfunction [1, 2, 7, 31, 47]. A recent meta-analysis of three randomized clinical trials showed a direct relationship between percentage of dorsal roots transection and functional improvement [33]. Functional improvement has been reported better when the operation is carried out before the age of 8 years, best between ages 3–5 years [7]. Patient selection and intense

physiotherapy support are important for the success of this operation.

Continuous intrathecal baclofen infusion (ITB)

Direct intrathecal delivery of baclofen has been employed for the last fifteen years, with proven satisfactory clinical effect [3, 4, 6, 14, 16, 18, 22, 23, 29, 30, 32, 34, 43, 51, 52]. As the effect of intrathecal baclofen may be unpredictable, a test lumbar infusion is performed in each patient who is a potential candidate, before a final decision is taken to implant a permanent indwelling pump. Intrathecal baclofen test is performed following percutaneous lumbar catheter insertion. The next morning a single baclofen injection is given usually 100 μg. In very thin patients often we start with 50 μg to avoid overreaction. Depending on the clinical response, dose escalation is performed the following days, to 75 (if started with 50), 100 and 200 μg [3, 6]. In most patients, the test with this maximum dose will clarify if they are suitable for pump implantation. Usually, a test is considered positive if improvement of at least one point in the Ashworth scale is seen in spasticity in the various affected joints. Often, the effect of baclofen can be checked with EMG (Electro-Myo-Graphy) [45]. Complications of the test include CSF leak around the lumbar catheter, aseptic or septic meningitis and baclofen overdose with respiratory compromise or arrest, if the lumbar catheter has been placed high in the spine. For this reason, physostigmine should always be available when baclofen injection is performed.

After establishing suitability of the patient, the pump system is installed surgically. Usually, the pump is installed in the subcutaneous tissue of the right iliac fossa, in a ''pocket'' that is excavated in the subcutaneous fat through a linear incision. In thin patients, weighing less than 30 kg, a variation of the technique allows implantation of the pump partly under the fascia of the rectus abdominis muscle. Through a midline lumbar incision centered around the L2-3 level, a Tuohy needle is used to introduce the lumbar catheter in the theca and advance it by 15 cm, to ensure catheter tip placement around the T9–10 level, in a fashion similar to inserting a lumbar-peritoneal shunt [24]. The lumbar catheter is tunnelled through the fat to the abdominal wound, and connected to the pump. The pump is primed with baclofen before implantation, and care is taken to carefully measure the length of catheter implanted, and subsequently calculate a bolus dose that will advance the baclofen from the pump to the catheter tip in 20 minutes, before establishing a slow injection at 24 hourly rate, equal to that of the successful test. After successful implantation, the dose is gradually increased to a level where satisfactory control of the spasticity is achieved without incapacitating weakness. It usually takes several weeks of dose alterations, increasing not more than 10% of the 24 hourly dose each time, before a satisfactory level is achieved. The pump requires refill every 6–12 weeks, depending on the level of the daily dose.

In the early dates of pump delivery systems, only fixed rate pumps were available. Such systems are still available and are commonly used in pain or chemotherapy treatment. A representative pump of this type is the Codman 3000 Infusion Pump (Codman, Raynham, MA, USA). Since the mid 1990s, adjustable pumps became available, which allow titration of the daily-administered dose percutaneously using computer driven telemetric equipment, which allows fine-tuning of the clinical result [3, 4, 6, 16, 23, 29, 30, 32, 52]. The most commonly used programmable pump system is the Medtronic SynchroMed (Medtronic Inc., Minneapolis, MN, USA) (Fig. 3). It has battery supply that lasts a nominal 5 years, and comes in two versions, the 18 and 10-ml, their difference been the height of the cylindrical metal enclosure, while their diameter is the same. The 18-ml version is used in adults and children over 30 kg, who have enough subcutaneous fat to support the bulky pump without encountering wound problems. The 10-ml version is designed for thin built children weighing less than 30 kg, who would not be able to accommodate the

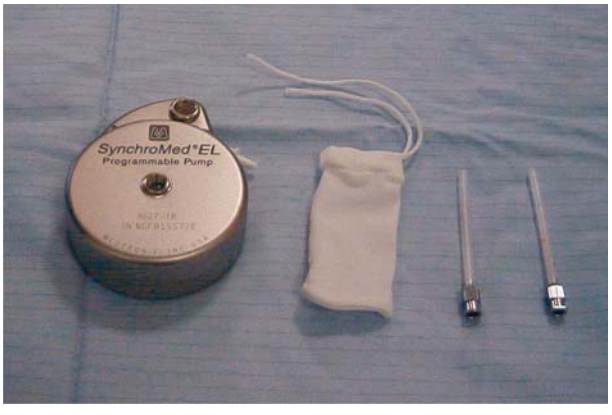

Fig. 3. Medtronic SynchroMed pump (Medtronic Inc., Minneapolis, MN, USA) seen just prior to implantation. The white cotton pouch seen in the middle is used to place the pump in prior to implantation in the subcutaneous fat ''pocket'' in order to avoid rotation of the pump and subsequent kinking or damage of the fine outlet catheter. The refill port can be seen in the centre of the upper surface of the pump. The two needles come with the insertion kit and are used to fill the pump with baclofen just before implantation. Similar needles are used for refilling

larger pump. Debate still exists on the long-term efficacy of intrathecal baclofen on patients with spasticity. Clinical series have demonstrated a good short-term response, with improvement of spasticity and a reduction in the corresponding need for orthopaedic surgery in children with spasticity due to cerebral palsy [22]. Inevitably, baclofen treats the effect of spasticity rather than the cause, acting on chemical receptors of the spinal cord, and for that reason there is potential for up or down-regulation of the receptors on which it acts with time. Available reported experience has demonstrated that the good effect can be present for a number of years, up to 10–15 so far [3, 4, 6, 23, 28, 30, 32]. Beneficial effect on quality of life issues has been recorded in patients treated with ITB [15]. Apart from spasticity, intrathecal baclofen administration has been shown to significantly improve dystonia as well [5, 50].

While ITB therapy has gained popularity in recent years, like all implant surgery, it is not without complications. A significant number of patients experience device-relate adverse events, to a rate of 0.5 per recipient year, half of which require surgical treatment to correct [16]. Non-device related complications occur at an average 1 per recipient-year, usually related to changes in dose, such as temporary significant decrease in tone after increase in dose or sudden increase in tone and baclofen withdrawal symptoms in case of poor refill timing or pump removal due to infection [19]. Implant infection occurs in approximately 10% of cases [4, 25]. Wound problems are infrequently seen, usually in very thin patients because the skin is stretched over the bulky pump and the wound edges become ischaemic and break down. Exacerbation of seizures, constipation and even acute pancreatitis after implantation have been reported [16]. Nevertheless, there has been a major push from the industry to facilitate establishment of intrathecal baclofen as a mainstream surgical option in the management of spastic CP, with considerable success so far.

Future developments

In neuromodulation, there is a definite trend away from ablative treatments and towards reversible stimulation and infusion systems. Current pumps are too big and cumbersome, require refilling every 3 months and hence they ''tie'' the patient to the hospital; by other 21st Century technological standards, they are rather less sophisticated than they should be. In the next decade, it is anticipated that technological improvements will render the pumps more patient friendly.

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Efficacy of intrathecal baclofen delivery in the management of severe spasticity in upper motor neuron syndrome

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Summary

In the treatment of patients with severe spasticity, intrathecal administration of baclofen (ITB) was introduced in order to exert its effect directly at the receptor sites in the spinal cord, and have better therapeutic efficacy with smaller drug doses compared to oral antispasmodic medications. Apart from our own research in Groningen, a review is performed to present and discuss the efficacy of ITB in patients with spasticity and hypertonia as symptoms of the upper motor neuron syndromes. The majority of the ITB studies describe proven efficacy in the reduction of spasticity and spasms in short-term and long-term follow-up. Functional improvements in daily care, hygiene, pain, etc are described but not often with reliable and validated instruments. A few studies reported significant improvement in walking performance in ambulant patients. The studies that have been done on the efficacy of ITB in relation to quality of life (QOL) showed some evidence of improvement. Future research is needed on fine tuning in the ITB therapy using functional assessment instruments.

Keywords: Neuromodulation; spasticity; baclofen; intrathecal pump; upper motor neuron syndrome; ITB.

Introduction

Spasticity in upper motor neuron syndromes

In patients with upper motor neuron syndrome (UMNS), impairments of muscle activation can develop in a variety of conditions. These impairments of muscle activation can be divided in *deficit* and *excess* symptoms. *Deficit symptoms* are caused by the reduction or loss of normal voluntary muscle function and can be defined by the presence of a paresis, loss of selectivity of movement, loss of dexterity of movement or enhanced fatigability [6]. *Excess symptoms* reflect the presence of abnormal muscle activation and contain spasticity and hypertonia but also co-contractions, involuntary synergies and abnormal reflex responses. Apart from these symptoms, changes in the biomechanical properties of the muscle-tendon complex such as muscle shortening can develop and will influence the movement disorder [16]. ***Spasticity*** is defined as "*a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes*" [18]. ***Hypertonia*** is defined as "*a non-velocity-dependent resistance to passive stretch*" which can be a symptom of abnormal muscle activation but also of developed changes in the biomechanical properties of the muscle-tendon complex.

In clinical practice, the term "spastic hypertonia" is often used and is almost equivalent to all the excess symptoms accompanying the UMNS. Spasticity is a dynamic process that is movement-dependent and therefore heavily and variably influenced by standing, walking and transferring. With respect to mobility, spasticity tends to slow it down, making walking more laborious and effortful and resulting in a progressive reduction in exercise tolerance. Severe spasms and hypertonia cause difficulties with sitting, transfers and ambulation resulting in skin problems and increased risk of falling. However, functionally, spasticity can also be the residual extension, which provides some stability for stance and walking. Spasticity and hypertonia are spinal in origin and arise principally from disinhibition of spinal reflexes caused by a lesion in the controlling supraspinal pathways that mediate their functions by release of neu-

rotransmitters. Modulation of these neurotransmitters provides the rationalisation of drug treatments for spasticity. The choice of treatment depends on the severity of spasticity and hypertonia, the impact on the patients abilities, the presence of focal versus generalized symptoms, the previous therapies and their side effects, the

Table 1. *Efficacy of ITB in patients with severe spasticity*

Study	Subjects	Design/follow-up	Assessment	Outcome
SCI and MS				
Penn et al. (1989) [27]	SCI: 10 MS: 10	Rd, DB, PC, CO 19,2 mo	AS, SFS	AS and SFS improved
Loubser et al. (1991) [19]	SCI: 9	DB, PC 3–22 mo	AS, SFS, Mob, ADL, BF	AS, SFS, Mob, ADL, BF improved
Hugenholtz et al. (1992) [15]	SCI: 4 MS: 2	DB, PC 30 days	AS, SFS	AS,SFS improved
Meythaler et al. (1992) [20]	SCI: 5 MS: 1 OSP: 4	DB, PC 12 mo	AS, SFS, Balance, Mob	AS,SFS, Mob, Balance improved
Penn (1992) [28]	SCI: 32 MS: 33 OSP: 1	open-label 30 mo	AS, SFS	AS, SFS improved
Coffey et al. (1993) [8]	SCI: 59 MS: 31 OSP: 1	DB, PC 19 mo	AS, SFS	AS, SFS improved
Azouvi et al. (1996) [3]	SCI: 12 MS: 4 OSP: 1	open-label 37 mo	AS, SFS, FIM, ADL	AS, SFS, ADL FIM-mob improved
Ordia et al. (1996) [25]	SCI: 27 MS: 26 OSP: 6	DB, PC in 9 subj. open-label in 57 subj.	AS, SFS, BF, Mob	AS, SFS, BF improved Mob improved in some
Middel et al. (1997) [23]	SCI: 12 MS: 10	Rd, DB, PC, CO 3–12 mo	AS, SFS, QOL: SIP, HSCL	AS, SFS improved, SIP, HSCL some items improved
Zahavi et al. (2004) [33]	SCI: 10 MS: 11	longitudinal follow-up 85 mo	AS, SFS, EDSS, ISS, AI, QOL: SIP, HSCL	AS, SFS improved ISS, AI decreased
Boviatsis et al. (2005) [5]	SCI: 7 MS: 15	open-label	AS, SFS, BI	AS, SFS, BI improved
Cerebral pathology				
Becker et al. (1997) [4]	ABI:18	open-label	AS, SFS, pain, nursing-care	AS, SFS, pain, nursing-care improved
Meythaler et al. (1999) [21]	ABI: 3 CVA: 3	Rd, DB, PC, CO 3 mo	AS, SFS, MoStr	AS, SFS improved, MoStr stable
Rawicki et al. (1999) [30]	ABI: 13 CVA: 2 CP: 3	open-label	AS, SFS, SHS	AS, SFS, SHS improved
Dario et al. (2002) [9]	ABI: 14	open-label	AS, SFS	AS, SFS improved
Francisco et al. (2003) [10]	CVA: 10	open-label 9 mo	AS, gait velocity	AS, gait speed improved
Rémy-Néris et al. (2003) [31]	ABI: 3	case series bolus baclofen	Gait velocity	gait speed improved
Horn et al. (2005) [14]	ABI: 28	case series bolus baclofen	AS, gait velocity	Gait speed improved
Albright et al. (2003) [1]	ABI: 14 CP: 54	prospective multicenter 10 years	AS	AS remained improved
Krach et al. (2005) [17]	CP: 31	open-label 12 mo	AS, GMFM	AS, GMFM improved

SCI Spinal cord injury, *MS* multiple sclerosis, *OSP* other spinal pathology, *ABI* acquired brain injury, *CP* cerebral palsy, *Rd* randomized, *DB* double-blind, *PC* placebo-controlled, *CO* cross-over, *mo* month, *AS* ashworth scale, *SFS* spasm frequency scale, *Mob* mobility, *ADL* activities of daily life, *BF* bladder function, *FIM* functional independence measure, *QOL* quality of life, *SIP* sickness impact profile, *HSCL* Hopkins symptoms checklist, *EDSS* expanded disability status scale, *ISS* incapacity status scale, *AI* ambulation index, *MoStr* motor strength, *SHS* Snow hygiene scale, *BI* Barthel index, *GMFM* gross motor function measure.

duration of the disease and finally, by the cost of the treatment. The aim of this review is to present and discuss the efficacy of ITB in patients with spasticity and hypertonia as symptoms of UMNS. The current opinions will be described.

Intrathecal baclofen

Baclofen (4-amino-3(p-chlorophenyl)butyric acid) is structurally similar to the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and acts on the $GABA_B$ receptors on the presynaptic nerve terminals to suppress the excitatory transmitter release involved in monosynaptic and polysynaptic reflexes [24]. Baclofen is a poorly lipophilic drug which transverses the blood–brain barrier insufficiently. In patients with severe spasticity, orally administered baclofen can not achieve sufficient concentration in the spinal cord to control spasticity because this would require high systemic concentrations and would be associated with brain-related side effects such as sedation, confusion and drowsiness.

When baclofen is administered intrathecally, it exerts its effect directly at the receptor sites in the spinal cord, resulting to greater therapeutic efficacy at smaller doses and thus, less systemic toxicity compared to oral administration [24]. The required intrathecal dose is about 100 to 250-fold smaller than the standard oral dose [19]. Continuous intrathecal baclofen (ITB) utilizing a subcutaneously implanted pump and an intrathecal catheter was introduced in the treatment of severe spasticity in 1984 [26]. Since then, numerous studies have confirmed the efficacy of ITB in patients with severe spasticity (Table 1). Most of these studies describe patients with spinal cord injury, multiple sclerosis, and brain injury [3, 4, 8, 9, 11, 14, 15, 19, 20, 21, 23, 25, 27, 28, 30, 33] (Table 1). Later studies were done in patients with cerebral palsy (CP) or stroke [1, 10, 13, 17, 22, 31] (Table 1). Patients who are considered for ITB therapy should have severe spasticity, unresponsive to oral medical treatments, which causes functional limitations interfering with transfers and ambulation. In addition, patients with painful spasms and problems with skin hygiene due to spasticity or hypertonia are, in principle, eligible candidates. Usually, it is the occurrence of unacceptable side effects that limits an increase of the oral dose of spasmolytic medication.

The responsiveness to ITB will be determined by a screening test in which the patient receives a single intrathecal bolus infusion of 50 μgrams baclofen. In special cases of severe dystonia or when fine tuning of the doses is desired to preserve ambulatory function, the baclofen can also be administered by continuous extracorporal infusion.

The responsiveness to ITB in the screening phase is considered satisfactory when it results to a decrease of the Modified Asworth Scale (MAS) score by at least one degree. After this, the implantation of the pump can be planned. The ITB pump is implanted into a subcutaneous pocket in the anterior abdominal wall and connected to a catheter which is tunneled subcutaneously and inserted into the spinal canal in the upper lumbar spine. The catheter tip is advanced up to the lower thoracic area. After the surgical procedure, the pump (Medtronic, Inc. Minneapolis, MN, USA) can be programmed in order to deliver the desired baclofen dose.

Assessment of outcome parameters

Since ITB administration was introduced for patients with severe spasticity unresponsive to other treatments, the early studies concentrated on outcome parameters related to the assessment of spasticity or hypertonia and the safety of the therapy. Muscle tone and spasms are assessed with the Asworth Scale (AS) or MAS and the spasm frequency scale (SFS) [2]. Also reflex scores, clone scores and electromyography have been used. Dependent of the study population, other assessments were performed such as bladder function, pain registration, hygiene scores and dependency on nursing care. ITB has proven its efficacy for the management of spasticity in patients with spinal cord lesions and brain-injured patients [3, 4, 8, 9, 11, 14, 15, 19–21, 23, 25, 27, 28, 30, 33]. The studies have consistently shown a significant decrease in spasticity and hypertonia as measured by the AS (average reduction of 2 in a scale of 5 points) and SFS (average reduction of 2 in a scale of 4 points). In addition, some functional improvements were recorded but often not by reliable and validated assessment instruments. However, in a clinical survey of forty centers with 936 pump implantations, improvements were reported in daily care such as easier dressing, transfers, wearing of orthosis, sitting tolerance, ambulation endurance, upper limb dexterity [32], liability to skin breakdown, and nursing care [4, 30].

In patients with cerebral palsy, the Gross Motor Function Measure (GMFM) was used to assess changes in motor function after ITB; in 2005, Krach reported a functional improvement due to the reduction in hypertonia [17]. However, assessments on how the disability affects the quality of life (QOL) were used sparsely if not at all [33]. A few studies used assessment instruments to evaluate disability outcome such as satisfaction

surveys, evaluation of functional abilities, evaluation of personal independence, functional independence measurement (FIM), and the Barthel index score [3, 5, 19, 33]. These studies reported significant improvement in activities of daily life (ADL), life comfort and mobility scores. Little attention has been paid to evaluating the effects on QOL in patients receiving ITB [7, 23]. Few studies have addressed the issue of functional improvement in all health-related aspects (impairment, disability and perceived health status) with long-term (longer than 2 years) use of ITB [3, 12, 33]. The FIM, QOL Index, Sickness Impact Profile (SIP) and Hopkins Symptom Check List (HSCL) have been used. Two studies reported significant increase of FIM and SIP scores [3, 12] while one study, with a mean follow-up of 7 years, found no significant increase in the perceived health status [33]. It should be mentioned that there are problems with the assessment of QOL during long intervals. First, the progressive nature of the disease and aging will affect the results of assessment of the perceived health status. It should be noted that the psychosocial dimensions are not only related to achieving adequate control of spasticity and spasms but to other factors. For example, patients suffering from complications relating to the baclofen pump could also influence negatively the psychosocial aspects of the perceived health status [33]. QOL will be determined in the context of reference to the patient.

Groningen research

A prospective multicenter trial was performed in which patients with intractable spasticity due to spinal pathology were treated with ITB and followed up for at least 5 years [23, 33]. During a 4-year period extending from 1991 to 1995, a programmable pump for ITB was implanted in 38 patients [23]. In the long-term follow-up (mean: 7 years), 21 patients were evaluated with assessment of impairments, disabilities and QOL [33]. The MAS, SFS, Expanded Disability Status Scale (EDSS), Incapacity Status Scale (ISS), ambulation index (AI), SIP, HSCL were used, and completed with a questionnaire to determine the overall satisfaction of the effects of treatment. Of the patients, 53% had multiple sclerosis, a progressive disease, and the other 47% had a non-progressive spinal cord disease.

In our study, the patients showed a significant improvement at the level of impairment (MAS and SFS, $P<0.05$). Surprisingly, a small but significant decrease was found at the levels of disability (EDSS and ISS, $P<0.05$) and in one psychosocial dimension, this of the perceived health status (SIP, $P<0.05$) at long-term follow-up. No significant differences between patients suffering from a progressive disorder versus those with a non-progressive disorder were found. In our experience, mean dosages of those patients suffering from a progressive disease are higher compared to those with a non-progressive disease but our analysis did not show a statistically significant difference [33]. All patients, except two, were satisfied with the overall treatment. The patients reported improvements in the increased ease of transfers, better seating posture, ease of ADL care, decrease in pain and in two patients a better walking performance. The two patients who were not satisfied experienced several complications (catheter dysfunction and acquired allergy to baclofen). In our study, we found a discrepancy between the subjective reported improvements at all levels of functioning and the significant decrease in ability and undetectable change of QOL in the long-term follow-up. It seems that the decrease of abilities was not clinically relevant and, as mentioned above, QOL assessment in a long-term follow-up could be confounded by other factors not related to ITB [33]. The side effects of baclofen were temporary and resolved with decreasing the dosage. The reported drug-related complications in our study were more frequent compared to other studies, possibly due to the fact that our patients were followed-up for a longer period. Temporary removal of the whole pump system was necessary in two patients because of meningitis in one and persistent fever due to bacteraemia in the other patient.

Ambulatory patients

The efficacy of ITB on severe spasticity in non-ambulantory patients with either spinal cord or acquired brain injury has become accepted worldwide. Functional improvements in daily care, hygiene, pain and prevention of complications such as skin erosions or ulcers are considered important benefits of the therapy. With respect to ambulation, spasticity tends to slow it, making walking more laborious and effortful. Spasms can make gait unsafe and cause problems with transfers resulting in an increased risk of falling. Nevertheless, spasticity is also the remaining extension ability that provides some stability in stance and walking. With respect to ITB in ambulant subjects, controversy exists because it could improve but also worsen walking performance.

Recently, studies were performed to investigate the efficacy of ITB on functional outcome in ambulatory

patients [11, 14, 31]. Two studies used computerized gait analysis to assess functional changes. The majority of their patients presented with hemiplegia or asymmetric tetraplegia. Gait characteristics were assessed before and after bolus ITB administration [14, 31]. These studies reported significant improvement in gait velocity (at preferred walking speed), stride length and kinematic data. However, there were subjects in whom these outcome measurements remained unchanged or even worsened. A substantial variability in individual patient responses to ITB was observed concerning gait characteristics [14]. An interesting phenomenon was the significant correlation between gait velocity pre-ITB and the observed increase in velocity after bolus ITB [14]. Patients with better baseline walking performance had a more favorable response to ITB. They were better able to adapt to changes in muscle tone and translate this into gait performance [14]. This outcome is also in accordance with the assumption that patients with minimal walking ability may depend more on their extension tone for standing and walking; thus, a reduction of this extension tone will diminish their ambulatory function. Gait velocity is not only a good outcome measure for ambulatory performance but it may also be a screening measure to predict potential functional improvement after ITB in ambulatory patients. Instrumental gait analysis could, therefore, be helpful as a functional assessment tool in the ambulatory patient group. In the early days of this treatment, there were concerns about the possibility of affecting the ambulatory function of patients with hemiplegia by weakening the muscles on the unaffected side. Studies of stroke patients however showed no clinically adverse effect on the strength of the unaffected limbs and the ability to ambulate [10, 22].

Dosing in ITB

Dependent on the rate of baclofen daily infusion, a periodic refilling of the pump reservoir (every 8–12 weeks) is necessary. In patients with severe spasticity, dose titration is carried out to decrease the spasticity to a level in which goals such as better sitting, transferring and nursing care are accomplished. In ambulant patients, titration of ITB dose is extremely important to reach a better functional level of walking. A great advantage of ITB therapy is the programmability; so individual functional goal setting is possible. Dosing can be modulated over the day, so one can have a higher dose of baclofen at night than during the day for the treatment of nocturnal spasms and at the same time maintenance of walking performance at daytime. In a long-term follow-up study, there was a trend towards higher required doses of baclofen in patients with a progressive spinal disease compared to patients with a non progressive spinal disease although this difference was not significant [33]. In addition, the required doses in spasticity of cerebral origin were higher compared to spasticity of spinal origin [29]. A wide range in the mean required daily doses of ITB from 100 to 500 μg with extreme lowest the 25 μg and highest the 1500 μg of required doses has been described [32].

Complications

Complications of the ITB treatment are described in almost all studies; they are divided in patient-, drug- or system-related. Patient-related complications include hypersensivity, cerebrospinal fluid (CSF) leakage, drug tolerance or intolerance and infection. Drug-related complications are mostly related to under- or overdose of baclofen and can be drowsiness, somnolence, nausea and vomiting, muscle weakness and epileptic seizures. Increases of spasticity or hypertonia are often associated with system-related problems; in such cases, the reason for the system failure must be determined. The most common cause of the system-related complications is the catheter malfunction. If the patient develops weakness, it should be questioned if this is real muscle weakness or an unmasking of a neurological deficit due to UMNS [29]. The relationship between ITB and epileptic seizures is a subject of further study and discussion [1, 29]. This complication appears in patients with known epilepsy and the frequency of seizures seems not to change after ITB [1]. In long term follow up studies, the frequency of complications is comparable to studies with a shorter follow up period [1, 29, 33]. The minor side effects such as CSF leakage, spinal headache, hypotension, somnolence, and constipation appear in about 50% of the patients while the serious complications such as overdosage, withdrawal syndrome, infection, and catheter malfunction in about 10–15% [29]. The most common reason for pump replacement is infection or the end of battery life [32]. Nowadays battery life is about 7 years. In spite of these complications and the need for replacement of the pump after 5–7 years, a great majority of the patients in long term follow studies were satisfied with the overall treatment [33]. They would advise this sort of treatment to other patients with spasticity. They would willingly undergo this treatment again if

necessary without being discouraged by the time and effort required and the complications inherent in this type of treatment.

Conclusion

Administration of ITB in patients with severe spasticity has proven its efficacy in reducing spasticity in assessments by the AS and SPS. This efficacy was maintained in long-term follow-up studies. Functional improvements in daily care, hygiene, pain and prevention of complications are often described but not always with reliable and validated assessment instruments. However, it was recently shown that ITB could be a potent neuromodulation instrument in patients with severe spasticity with preservation or improvement of walking performance. The efficacy of ITB in relation to QOL has not been studied extensively but the studies, so far, have shown some evidence of improvement in QOL. There is, however, debate regarding: a) how adequate the assessment of the QOL can be, and b) the influence of the length of the follow-up period on the QOL in progressive versus non-progressive diseases [3, 23, 33]. In respect to QOL, further research is highly needed and should be focused on comparisons of the patient's expectations and post-ITB experience as a measure of patient's satisfaction regarding ITB. In the context of neuromodulation, fine tuning of ITB doses is very interesting especially in patients with preserved functional abilities. In the future, the real challenge will be to focus prospective studies on tuning in the ITB therapy using more refined functional assessment instruments such as instrumental gait analysis or other motor functional assessment scales.

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Intrathecal baclofen in the treatment of spasticity, dystonia and vegetative disorders

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Summary

Baclofen (β-p-chlorophenyl-GABA) binds to a number of spinal and cerebral sites and depresses the excitability of motor neurons. Intrathecal administration induces much higher CSF concentrations compared to the limited passage through the blood-brain barrier after oral administration. The development of reliable implanted pumps allows long-term intrathecal baclofen treatment (ITB).

Baclofen is mainly an antispastic drug and the main indication of ITB is generalized lower limb spasticity in spinal cord injury and multiple sclerosis. The side-effects are due to either drug over-dose or withdrawal and to malfunctions of the implanted device (disconnections of the catheter, infections, etc). Large numbers of patients have been treated over the past twenty years.

More recently, baclofen has been used in the treatment of spasticity of cerebral origin, and in the treatment of other motor disorders, mainly dystonia. The results in cerebral palsy are promising and ITB's role will probably grow in the management of the movement disorders of these children.

Further studies are required on the exact site of action, on the possible association with other drugs, especially clonidine and on the development of sustained release formulations.

Keywords: Neuromodulation; spasticity; baclofen; pump; ITB; cerebral palsy; dystonia; vegetative state.

Introduction

Baclofen or β-p-chlorophenyl-GABA is a $GABA_B$ receptor agonist and one of the most widely used oral antispastic drugs. The therapeutic effect is often moderate, due to limited passage of the brain-blood barrier, resulting in very low concentrations in the cerebrospinal fluid (CSF) after oral intake. Large systemic doses also lead to side effects such as drowsiness and confusion. In 1984, Penn and Kroin [27] first introduced intra-thecal administration of baclofen (ITB).

The efficiency of the intrathecal route and the development of reliable pumps now position ITB as one of the main options for the treatment of severe lower limb spasticity and provide an effective alternative to other surgical procedures such as rhizotomy and DREZ tomy. Lower limb spasticity of spinal origin was the first indication of ITB. The large published series include mainly patients with spinal cord injuries and multiple sclerosis [16, 28, 37]. More recently, patients with spasticity of cerebral origin have been treated, including adults and children with cerebral palsy [15, 17, 19, 20], acquired brain injuries [1, 5] and cerebro-vascular deseases [18, 23, 31]. Clinical, pharmacological and electrophysiological data also suggest that ITB could be effective in other motor disorders, especially dystonia [36], in certain types of pain [35] and in vegetative states after severe brain injury [6, 10].

Baclofen is a racemic mixture and the active component is L baclofen. It binds to $GABA_B$ receptors that are found on the terminals of primary afferents but also on the terminals of descending fibres and on the soma of the motoneuron itself. Recent electrophysiological data does not support the hypothesis that the antispastic effect of baclofen is mainly related to increased presynaptic inhibition [4, 26]. Alternatively, it could be related to increased inhibition on other pathways such as disynaptic Ib inhibition or recurrent inhibition. It also seams probable, that at least part of the antispastic effect, is due to direct binding of Baclofen on motor neuronal $GABA_B$ receptors, inducing an overall decrease of motor neuronal excitability. This effect is in fact not a specific

''antispastic'' effect and could account in part for the effect of ITB on other motor disorders. It may also explain why it can be difficult to adjust baclofen doses and achieve both sufficient reduction of spasticity and preservation of voluntary movements. Other sites of action have been also demonstrated. Both GABA and baclofen inhibit the release of Glutamate and Substance P from the primary afferents. GABA is involved in regulating sympathetic output in spinal pathways [35]. This could explain the analgesic effects of baclofen, that seem in part to be independent from the reduction of spasms, and the effect on vegetative disorders. Baclofen also binds to other cerebral sites. Their exact role in the effect of baclofen on motor disorders of cerebral origin is unknown.

Continuous administration of ITB results to 4/1 ratio of concentration in the CSF compared to the cerebral ventricles. This explains the major effect on lower limb spasticity, the reduction of centrally mediated side-effects and the need for upper thoracic or cervical implantation of the catheter tip when upper limb or trunk spasticity should to be treated.

Treatment procedures, including test procedures, pump and catheter implantation, filling visits and follow-up are largely independent of the indication. The functional goals, evaluation procedures, and indications of ITB compared to other available techniques are specific for each clinical condition.

ITB treatment: procedures

Patients should be selected for ITB through multidisciplinary clinics. The evaluation must include the consequences of spasticity on abilities, comfort and quality of life. Spasticity rating using the Ashworth scale or the Penn scale for the spasm rating and evaluation of the range of motion evaluation are necessary but are not sufficient in order to select a patient for ITB.

Patients can be divided into two large functional groups depending on whether they have or have not lost the ability to walk. In ambulatory patients, pre-treatment assessment should include simple functional parameters such as comfortable gait speed and maximum walking distance as well as video and EMG gait analysis. In wheelchair dependent patients, the assessment mainly relies on the quality of sitting position, the comfort in bed and wheelchair, the difficulties with personal hygiene, dressing and transfer.

The next step is that of test injections. They can be performed by lumbar puncture, or after introduction of an intradural catheter that may be connected to a subcutaneous reservoir or used directly. In this case, the injection tests can be bolus injections or continuous perfusion via a continuous infusion device. Lumbar punctures can be difficult in cases of severe trunk spasticity or in children. Intrathecal catheters increase the risk of infection but allow finely tuned dose adjustments and better evaluation of gait in walking patients. Test doses start at 25 or 50 μg and increase up to 200 μg depending on the clinical effect. Continuous perfusion tests allow higher test doses and mimic more closely the effect of the treatment in the long term. Test injections usually reduce the Ashworth score by 1–2 points. If the functional goals that have been set before the test are achieved, the patient is referred for implantation.

The catheter is inserted via a Tuohy needle and its tip placed at the appropriate level. Level choice depends on the presence of trunk and upper limb spasticity. The catheter is tunneled and connected to the pump. The pump is placed in a subcutaneous pocket in the abdominal wall. Several types of pump are available on the market with their volume of reservoir varying from 10 to 40 ml. Implantation is technically possible in children above 10 kg [17, 20]. The pump is filled via the septum which can be located by palpation or using a guide. Filling is necessary every four to sixteen weeks, depending on the volume of the reservoir and the daily dose, which varies from 50 to 1000 μg. Inter-patient variability is high. Required doses tend to be higher for the treatment of spasticity of cerebral origin. A two-three fold increase in required doses is usually observed during the first year. After this period, the required doses become stable [28]. The devices presently used are programmable pumps and can be set to continuous infusion mode or complex modes including periods of different dosage and bolus injections. Some pumps have a separate access port to the catheter which can be used for bolus tests. The pump is programmed via external software and the data is transferred by a hand held radio frequency telemetry wand. The batteries work for 4–8 years depending on the infusion rate. The pump must then be replaced. The pumps have two separate alarms. The reservoir alarm will ring if the reservoir volume is below a threshold value. The second alarm will ring if the battery is empty. The pump must be stopped when the patient undergoes MRI investigations.

Complications may occur because of the pharmacological effects of baclofen or the presence of an implanted device.

Overdose induces somnolence and respiratory depression and can lead to respiratory arrest [11]. Close mon-

itoring of respiratory parameters is necessary after test injections. After pump implantation, overdose is most often due to errors in concentration, unwanted dosage modifications, or erroneous injection via the catheter access port instead of the reservoir. Pump dysfunction leading to over-infusion has not been reported. Treatment of overdose is symptomatic.

Acute baclofen withdrawal is also potentially life-threatening [9]. Generalized itching in a patient on ITB can be the first sign [7]. Patients then present with rebound spasticity, decreased level of consciousness and vegetative dysfunction (tachycardia, hypotension, hyperthermia). Differential diagnosis with autonomic dysreflexia, and neuroleptic malignant syndrome may be difficult. The main causes of acute withdrawal are errors in the filling procedure, and catheter disconnections. Withdrawal syndrome due to low residual volume has also been described [32]. The treatment of acute withdrawal is based on administration of baclofen, if possible via the pump, or orally, at high doses. Other GABAergic drugs such as benzodiazepines may be used [9, 24]. Patients should be aware of the effects of acute withdrawal and be provided with oral baclofen for the eventuality of pump malfunction.

Minor side-effects may occur transiently after pump implantation. The most frequently observed are pain, and paresthesia in the lower limbs and irregularity of micturition. The reduction of muscle tone and the decrease of activity due to hospitalisation may induce the risk of thrombophlebitis that should be prevented.

Complications may also occur due to the implanted device. The most frequent problems are disconnections and kinks in the catheter, causing a decrease in the effect and possibly a withdrawal syndrome. Despite improvements in the devices, especially in the connections between catheters and pumps, these incidents remain frequent [10–25%) and may occur repeatedly in the same patient [28]. They are especially frequent in active patients who perform multiple transfers, engage in sports activities, or walk. Recently Ross *et al*. [33] described the possible implantation of the pump in the paravertebral area in order to reduce the length of the catheter and the catheter/pump movements. Standard X-rays may show the disconnection or kink.

Infectious complications occur in 10–15% of cases. These may occur in the days following the surgical procedure or after a refilling injection. In our experience, infectious complications are more frequent in traumatic brain-injured patients, who often also have gastrostomies and/or tracheotomies. In such patients, the pump can be placed in a more lateral position. The filling kits now include anti-bacterial filters. The treatment relies on antibiotics and unfortunately, often on removal of the pump. Maintaining the pump and infusing antibiotics in the pocket and/or through the pump has been described as a possible alternative [8].

Patients and caregivers should be informed regarding the risks of drug overdose and withdrawal, the function of the pump (volume of reservoir, threshold of alarm, date of previous filling, date of next visit) and carry information concerning treatment, follow-up and dose adjustments.

Recent studies have addressed the possibility of sustained release formulations of baclofen [21]. Preliminary results have been obtained in the rat and show that therapeutic concentrations can be maintained one month after a bolus injection. This would allow tests on a longer period and in the usual living environment. It could also allow ITB treatment in non-stationary situations such as the acute phase of traumatic brain injuries, the terminal phase of paraplegia of tumoral origin, or in amyotrophic lateral sclerosis.

ITB treatment in lower limb spasticity of spinal origin

Spinal cord injuries and multiple sclerosis are the main indications for ITB in large series. Patients with spinal cord tumours and paraplegia of genetic origin have also been offered ITB treatment. Most frequently, the patient is wheelchair dependant and presents with flexion or extension spasms and/or spasticity of the adductors. The functional objectives most often include the treatment of painful spasms, improvement of sitting position, and easier transfer, personal hygiene, dressing, and performance of self-intermittent catheterisation as well as prevention of pressure sores. The medico-economic benefits of ITB have been documented; ITB may reduce patient's dependence and the number of required aid for activities of daily living [34].

ITB is less often used to improve the quality of gait in ambulating patients and such indications require continuous infusion tests. These tests may show whether the spasticity on extensor muscles is useful for transfers and gait and should not be treated. In quadriplegic patients, the upper-thoracic location of the tip of the catheter allows some effect on upper limb spasticity. ITB may interfere with reflex erection and ejaculation [12].

In spinal cord injured patients, intrathecal administration of clonidine has also been tested. Clonidine selectively depresses II afferents; their participation in

spasticity is probably more important than first thought [30]. Clonidine also reduces detrusor hyperactivity. Clonidine/Baclofen mixtures have been tested; this could be a future direction in the treatment of spinal cord injured patients who suffer from both spasticity and detrusor hyperactivity [3].

ITB in spasticity of cerebral origin

Since the 1990s, ITB has been proposed in the treatment of hypertonia in cerebral palsy [15, 17, 19, 20]. Again, the main objectives are improvements in gait, improvement in comfort and nursing in wheel-chair dependent patients. In children with cerebral palsy, the objective may also be the prevention of long-term consequences of spasticity on skeleton maturation and orthopaedic status. Studies show a decrease in the number of orthopaedic surgical procedures in patients treated with ITB [15], and prevention of complications such as hip migration [20]. ITB should be considered for patients with generalized hypertonia, particularly before deformities occur. As soon as the weight and body shape of the child allows, an early implantation with the smallest pump volume is probably worthwhile.

In older children or adults, ITB may greatly alleviate spasms and should be considered as an alternative to or as an adjunct to orthopaedic procedures. Effective treatment of spasticity may reduce very significantly the complications after hip replacement in patients with painful hip migration. In these conditions, the main challenge is the organisation of proper multidisciplinary clinics so that any such child or adult can benefit from the correct collaboration of orthopaedic and neurosurgical specialists.

In ambulatory children, the indications of ITB in combination with multi-site orthopaedic surgery remain under debate. For technical reasons, the implantation of an ITB pump should be considered before spinal arthodesis is performed for the treatment of scoliosis.

ITB has also been evaluated in the treatment of generalized hypertonia after traumatic or anoxic brain injuries [5]. The effect is not as dramatic as in spinal cord lesions. Nevertheless, several recent series document the potential benefit from ITB, even in patients in very poor motor and cognitive condition. The mean required doses tend to be higher and this justifies bolus test injections up to 300 µg, and/or continuous infusion tests before concluding that ITB is not effective. The time course of the effect may also be different with the maximum effect occurring after a latent period of 4 hours [29]. Although baclofen does reduce the epileptic threshold, ITB can be proposed for patients receiving anti-epileptic treatment.

Data concerning the potential effect of ITB in hemiplegia after cerebro-vascular accidents (CVA) is still quite scarce [14, 23, 25, 31]. In most cases, the objective is the recovery or improvement of gait in patients with generalized lower limb spasticity. Preliminary results show that ITB does not induce controlateral motor weakness. The improvement in gait parameters such as the duration of monopodal stance has been documented. Further large studies are necessary. The most frequent situation after CVA is limited foot spasticity which is efficiently treated by focal surgical neurotomies or botulinum toxin. ITB will remain limited to a small number of patients with generalized lower limb spasticity.

Effect of ITB on other motor disorders

The use of ITB on dystonia and various other movement disorders has also been reported in recent studies [2, 13, 22, 36]. These effects can be associated to the effects on hypertonia in children with cerebral palsy. The evaluation should include all aspects of movement disorders. Dystonias can be segmental or generalized and either primary (in many cases, genetic in origin) or secondary. Case reports have illustrated the effects of ITB on focal dystonia, after insufficient results from botulinum toxin treatment [13]. In focal dystonia involving the neck and upper limb, the catheter tip position should be cervical. ITB seams to be more efficient in secondary generalized dystonias. The doses are similar to those used in the treatment of spasticity. The site of action remains debatable. If the site of action in the spine is the final common motor pathway and the motorneuron itself, the spinal effect of baclofen may be fairly independent of the exact mechanism of action on hypertonia; this could account for the efficiency of baclofen even in dystonia of cerebral origin. The action of baclofen on cerebral sites has also been debated and could explain why baclofen administration can be ineffective after lumbar bolus injections whereas it can be effective after continuous infusion tests or pump implantations.

Effect of ITB on vegetative disorders

Vegetative dysregulation is frequent at the acute phase of traumatic brain injury (TBI). The treatment is difficult and often requires the use of neuroleptics and diazepines, inducing sedation. Several case reports or small

case series show the effect of ITB on these conditions [6, 10]. The treatment can be administered via a lumbar catheter as in other indications or directly into the ventricles. The reduction of the vegetative episodes occurs within a few hours. The exact site of this effect is not completely clear, and could involve spinal receptors regulating sympathetic outflow. The effect of early ITB on the overall evolution of brain injury is not known.

Use of ITB as analgesic treatment

Treatment of spasms can in itself reduce pain, and improve sleep. Recent clinical and neurophysiological data also suggest that baclofen could reduce pain by other mechanisms and be effective, particularly, in the treatment of neuropathic pain [35]. Both the antispastic and analgesic effect can be useful in the management of multiple sclerosis patients. In such conditions, the potential benefits and the mechanism of combined action of baclofen and morphine should be explored. The use of baclofen in the treatment of isolated neuropathic pain syndromes has also been described but remains limited.

Conclusions

ITB has a well-documented antispastic effect; it reduces lower limb spasticity by an average of 1–2 points on the Ashworth scale. It is now the main treatment of severe lower limb spasticity in patients with spinal cord injury and multiple sclerosis. In these conditions, further improvements will come from developments of the implanted devices (larger pumps with increased autonomy for adults, smaller pumps for children, secure catheter/pump connections), and from the use of drug combinations and sustained release formulations.

More recently, ITB has been proposed as an effective treatment in other conditions, particularly, spasticity of cerebral origin. The most promising results have been reported in series of children with cerebral palsy. ITB could be effective not only on spasticity but also on other movement disorders, particularly dystonia. Early treatment could prevent the complications of spasticity on the orthopaedic status and reduce the need for later orthopaedic procedures. The exact place of early ITB in the sequence of other corrective surgical procedures in these patients remains under debate and further studies are necessary. Considering the frequency of cerebral palsy, this indication could be the main future development for ITB.

In focal dystonia, vegetative disorders due to brain injury, and neuropathic pain, ITB can be useful; however, for the foreseeable future, it will probably remain a second-line treatment to be used following the failure of other procedures.

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Intrathecal baclofen in the management of post-stroke hypertonia: current applications and future directions

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Summary

This chapter will review the application of intrathecal baclofen (ITB) in the management of post-stroke hypertonia, a major complication that results in deformity and discomfort, and limits mobility and performance of activities of daily living (ADL). Initially, ITB was considered only in conditions characterized by severe multi-limb spastic hypertonia in non-ambulatory individuals. Lately, ITB is used in persons with stroke who can ambulate, with the intent of further improving walking ability. Early clinical experience and evidence suggest that when used in the appropriate patient, ITB is efficacious and safe in managing post-stroke hypertonia in individuals of various functional levels. This chapter will also review clinical situations that are common in the stroke population, which may influence treatment decision choices. There are still ample opportunities to conduct research on this treatment modality, especially in the areas of patient selection and outcomes in the stroke population.

Keywords: Spasticity; stroke; intrathecal baclofen.

Intrathecal baclofen

The intrathecal administration of baclofen is a noteworthy advancement in the management of post-stroke spastic hypertonia. It offers another option to oral medications, which may be ineffective in severe, generalized spasticity, or not well tolerated because of a myriad of adverse effects on arousal and cognition. ITB also is an excellent alternative to chemodenervation with phenol, alcohol, and botulinum toxin, whose effects are best seen in focal spastic hypertonia.

Baclofen is a GABA-B agonist that is believed to act by initiating a cascade of events that lead to hyperpolarization of neurons, blocking of calcium influx, enhancement of potassium conductance and inhibition of release of excitatory neurotransmitters [13]. This results in presynaptic inhibition, and decreased mono- and polysynaptic reflex and gamma motor neuron activity. Clinically, this is manifested as a reduction in the abnormal muscle tone and the hyperexcitability of stretch reflexes.

Baclofen is a poorly lipophilic drug, and thus, its access to the blood–brain barrier is limited. As a result, high doses of the drug are needed if it is administered orally or enterally in order to reach a significant concentration in the cerebrospinal fluid (CSF). High doses of baclofen correlate with the occurrence of adverse events, such as sedation, dizziness and drowsiness. As expected, persons with stroke and other acquired brain injuries, who already suffer from disorders of arousal and cognition, cannot tolerate high doses of oral baclofen well.

However, when administered directly into the CSF, even small doses of baclofen can reach a high concentration at its spinal site of action. Once in the intrathecal space, baclofen admixes with CSF and infiltrates the superficial layers of the spinal cord, where the drug binds GABA-B receptor sites to exert its effects. Intrathecal administration of baclofen obviates the need to penetrate the blood–brain barrier, and thus only a small dose is needed to achieve clinically beneficial results. It is estimated that when administered continuously in the intrathecal space, baclofen's CSF concentration is 50 times greater than an oral dose that is 100 times greater [14, 21]. As a result, only a few hundred micrograms of baclofen per day is needed to exert clinical effects, unlike the oral form, which needs to be administered in doses as high as over 100 mg/day. [14]. Thus, the occurrence of dose-related adverse events with intrathecal administration of baclofen is dramatically less than with the oral route.

Kroin and Penn [17, 18] demonstrated that the baclofen concentration in the lumbar and cisternal segments had a ratio of about 4:1, when simultaneously obtained

samples of CSF were measured during continuous infusion. This finding is noteworthy, as it explains the commonly observed superior effect on hypertonia in the legs as opposed to the upper limbs.

Motor dysfunction in stroke

Following a stroke, various motor impairments are observed. On one hand are deficits characterized by weakness and incoordination, and on the other, hypertonia, dystonia, co-contraction of agonist and antagonist muscles, and exaggeration of stretch reflexes. Functional impairments result from a combination of these motor abnormalities. Thus, a multi-modality rehabilitation approach is ideal in order to address each component of the over-all motor dysfunction. Weakness and incoordination are best managed by physiotherapy and other physical modalities, and although spastic hypertonia and dystonia may be influenced to a certain extent by physical treatments, they are best controlled by pharmacological interventions. Frequently, rehabilitation efforts are hampered by hypertonia, thus lessening a person's chances of reaping benefit from a therapy program unless the overwhelming hypertonia is sufficiently managed. In persons with stroke, who have residual ability to walk, hypertonia may result in gait deviations that further stress the joints and cause discomfort, thus disallowing ambulation over longer distances.

ITB therapy: patient selection and clinical indications

Candidates for ITB therapy are persons with post-stroke hypertonia that involves multiple joints primarily in the lower limbs, have significant limitation in function, and are either refractory to other pharmacologic and physical interventions, or are unable to tolerate the adverse effects of oral drugs (Table 1).

Candidates for ITB therapy can be further classified into those who have the potential for further functional improvement (''high-level group'') and those whose treatment goals are primarily for hygiene, comfort, and prevention of further deformities and complications (''low-level group''). The ''high-level-group'' includes those persons who are ambulatory or whose mobility is limited by spastic hypertonia and its concomitant motor problems. They typically have gait deviations and clonus that interfere with safe transfers and ambulation. Individuals in the ''low-level group'' include those with painful spasms and severe hip adductor spasticity that prevents perineal care, and are recalcitrant to other treatment modalities.

Table 1. *Indications for ITB therapy in the post-stroke hypertonia*

Severe, multi-joint spastic hypertonia, especially of the lower limbs
Spastic hypertonia that limits function (ADLs, mobility)
Spastic hypertonia that interferes with care and hygiene
Spastic hypertonia that is refractory to other treatment modalities
Painful spasms
Inability to tolerate side effects of other treatment modalities
Presence of risk for complications, such as contracture and pressure sore

Regardless of the potential for functional improvement, patients should be medically stable (e.g., infection-free and without active medical issues) and can be safely taken off anti-coagulant medications during the screening and implantation. There is no consensus yet as to how to manage those on anticoagulation, but a common practice is to defer ITB therapy until the patient can be safely taken off anticoagulants for the ITB pump implantation, unless alternative medications can be used in the meantime.

Special consideration must also be paid to those with poor trunk control, since a decrease in hypertonia typically unmasks latent weakness. The same is true for those with severe pre-existing gastrointestinal or bladder motility problem, and seizures, because baclofen may unmask pre-existing neurogenic bladder and bowel dysfunction [16] and lower seizure threshold [15, 24].

Patient assessment/goal setting

Clinical assessment tools, such as goniometric measurement, Ashworth scale (AS) [1], modified Ashworth scale (MAS) [2], and the Tardieu scale [3, 26], have been used to define spastic hypertonia in objective terms. These scales however are not purely objective, as they largely depend on the tester's performance and interpretation of findings, and are not adequate for the purpose of measuring spastic hypertonia. The AS, for instance, ignores the velocity-dependent nature of the tone abnormality, which is an accepted feature of spastic hypertonia, and although the Tardieu considers velocity-dependent tone, it misses the ''dynamic'' component, which is not manifested at rest. In persons with spastic hypertonia and dystonia, the latter contributes to the dynamic element of the dysfunction. Thus, it is not uncommon that an individual with stroke will have no abnormal tone or deformity in the ankle at rest, but once that person stands or transfers, the ankle goes into severe equinovarus positioning. This frequent observation cannot be measured by conventional clinical scales, which

are always performed at rest. Laboratory motion analysis is helpful, but is not widely available to the average clinician. The same can be said of electrophysiologic and biomechanical assessment techniques, which have been used primarily for research.

These challenges should not discourage clinicians in assessing the functional impact of spastic hypertonia and making treatment decisions based on solely on clinical data. Clinicians should not lose sight of what matters most to persons with post-stroke hypertonia: the impact of hypertonia on health status, functional ability, and quality of daily living. ''Pseudo-objective'' assessment scales should not constrain clinicians from moving toward a functional approach in assessing post-stroke hypertonia. Pain, difficulty with transfers and nursing care, and problems with activities of daily living (ADL), such as dressing and ambulation, should be assessed closely.

Since the impact of spasticity varies from person to person, goals need to be individualized and should depend on the patient's current and potential function. In ambulatory stroke survivors, goals should include enhancing gait speed and pattern, decreasing required assistance, and upgrading ambulation surfaces and stair negotiation. In those who are unable to walk, goals should include prevention of complications, such as contractures and pressure sores, facilitation of perineal hygiene and nursing care, wheelchair positioning and control of painful spasms.

Whatever the goals may be, they should be realistic. They should also be mutually agreed upon by the clinician and the patient and caregiver. It must be stressed early on that ITB therapy is not curative, but is an important treatment adjunct to try to reverse functional impairments imposed upon by spastic hypertonia, and with the help of other rehabilitation therapies, increase the likelihood of achieving functional potential.

Patient/caregiver education

Once identified as a candidate, the patient and caregiver should be educated on ITB with emphasis on the longitudinal nature of the therapy. Treatment goals, advantages of ITB over other treatment modalities, purpose of the screening trial, likely outcome of the screening trial and pump implantation, and potential complications should be reviewed. A psychosocial assessment of the patient and caregivers should also be performed to assess the level of motivation and ability to commit to follow instructions for maintenance therapy, including pump refills and need for adjunctive therapies, such as botulinum toxin injections and nerve blocks for residual upper limb hypertonia, and other physical interventions. This step is critical because the commitment of all individuals involved is necessary for the success of this therapy [20].

Screening trial

In order to enhance the prediction of ITB therapy outcome, a screening trial, either bolus or continuous, is recommended to demonstrate improvement in muscle tone and impact on functional capabilities. Baclofen is delivered either as a single bolus or as a continuous infusion intrathecally via a lumbar puncture or intrathecal catheter. The typical bolus dose is 50 μg. If there is no response to the first dose, it can be increased by 25–50 μg increments every 24 hours, up to a maximum of 100 μg. An average of one-point drop in the AS scores in the tested limbs is widely regarded as a ''positive'' response. Frequently, however, AS scores do not change dramatically, but functional enhancements are demonstrated, as in improved ambulation, quality of movement, and ability to perform functional tasks, such as bed mobility and transfers. This should also be considered as a ''positive'' indicator. In the United States, continuous screening trials in adults with stroke are rarely performed.

The onset of action of a single bolus dose of baclofen is about two hours, with peak effect at about four to six hours. The patient and caregiver should be cautioned of potential unmasking of weakness once abnormal muscle tone is controlled, and re-assured that this occurrence is limited to only about six to eight hours, or until the effect of the drug subsides. Initially, there was concern that the non-affected side may be weakened by intrathecal baclofen. Interestingly, studies in individuals with hemiplegia demonstrated that although abnormal tone improved on the affected side, there was no adverse effect on the strength of the contralateral, unaffected limbs [20, 10].

Perioperative management

The patient should be medically stable and infection-free. Attempts to wean oral spasmolytic medications need to be considered prior to pump implantation in order to lessen the potential additive spasmolytic effects of ITB. Pump placement site should be evaluated based on individual factors, such as wheelchair arm position, belt line, transfer techniques, and level of physical activity.

Goals of treatment and the patient and caregiver's commitment to share the responsibility in pump maintenance and dose adjustments should be reviewed, and further education regarding what to expect after the pump is implanted, including the expected benefits, potential complications, should be reviewed once more.

Pump implantation and maintenance

ITB therapy consists of surgically implanting a pump that infuses baclofen directly into the CSF. The pump is implanted within and sutured to a subcutaneous pocket in the anterior abdominal wall, typically under general anesthesia. Under fluoroscopic guidance, a catheter is introduced in the upper lumbar spine and advanced cephalad to the thoracic area. The distal end of the catheter is subcutaneously tunneled to the pump site. ITB pump placement, unlike rhizotomy, is a non-destructive and reversible surgical procedure. Pressure dressing, abdominal binder, and lying flat in bed for about 24 hours should be considered in order to minimize the risk of CSF leak. Following implantation the pump can be programmed to deliver baclofen as a continuous infusion.

Dose titration should not be done more frequently than every 24 hours in order to allow enough time to observe clinical response to a specific dose. Prior to discharge, instructions for wound care should be given to the patient and caregiver. They should be advised to avoid excessive trunk flexion and rotation during the first few weeks after implantation to avoid potential problems, such as pump flipping and catheter dislodgement.

Outcomes

Meythaler *et al*. [19] first demonstrated that ITB was effective in reducing spastic hypertonia in six subjects with acquired brain injuries. Three stroke and three brain injury survivors with ''spastic/dystonic'' hemiplegia of at least six months duration were screened for response to ITB in a randomized, double-blind, placebo-controlled manner, and received a bolus intrathecal injection of either 50 μg of baclofen or placebo. Those who had an average drop of two points in the AS were considered for ITB pump implantation. At three months after ITB implantation and at an average dose of 205.3 μg/day, there were clinically and statistically significant decreases in the AS, spasm frequency and reflex scores in the hemiplegic lower limb. The same improvement was observed in the involved upper limbs, but of lesser magnitude. Complications were minor, and included urinary hesitancy that improved with dose adjustment (Table 3).

The same investigators [20] showed that ITB was effective in reducing spastic hypertonia in persons with post-stroke hypertonia. Twenty-one subjects were screened in a manner similar to the earlier study, and those who had an average drop of two points in the AS proceeded to ITB pump implantation. About 12 months after ITB treatment, at an average dose of 268 ± 175 μg/day, there were clinically and statistically significant decreases in the AS (from a mean of 3.7 ± 1 to 1.8 ± 1.1; $p < 0.0001$), spasm frequency (from 1.2 ± 1.3 to 0.6 ± 1; $p = 0.4282$), and reflex (from 2.4 ± 1.3 to 1.0 ± 1.3; $p < 0.0001$) scores in the hemiplegic lower limb. The same improvement was observed in the involved upper limbs, but of a lesser magnitude. Moreover, motor strength of the uninvolved, or ''normal'', limbs was preserved. Three wheelchair-dependent subjects had dramatic improvement in gait, becoming able to walk independently or without an assistive device.

A case series of 10 ambulatory stroke patients [10] described further improvement in walking speed following ITB therapy and physical therapy. Gait speed improved from 36.6 to 52 cm/sec ($p = 0.0051$) at about nine months after ITB pump placement. Improvements in functional walking categories, as described by Perry [22], and certain functional mobility measures confirmed the effects of ITB therapy in motor functioning of persons with post-stroke hypertonia. In this case series, it appeared that those who had the best outcome were the subjects who had the best walking speed prior to initiation of ITB therapy ($r = 0.85$, $p = 0.0016$).

Recently, a multi-center, open-label investigation in the United States was completed. This is thus far the largest series of stroke patients who received ITB for spastic hypertonia. Initial reports described improvement in AS and FIM scores, as well as, scores on the Sickness Impact Profile, a quality of life measure [9].

Table 2. *Rehabilitation guidelines after ITB pump placement*

Start with a clean plate: re-assess the patient as ''new''
Elongate shortened tissues, through stretching, serial casting or surgery
Initiate strengthening program
Attempt to re-establish motor control and coordination
Re-evaluate orthosis, adaptive equipment, and seating system
Upgrade home program and family training
Employ other anti-spasticity pharmacologic treatment (e.g., botulinum toxin injections to treat residual focal spasticity), if needed, to optimize functional outcome

Enhancing results: maintenance therapy

Maintenance of the ITB pump includes dose titration, modifying drug delivery technique, and periodic refilling of the pump reservoir. The goal of dose titration is to deliver the optimal amount of baclofen sufficient to control, but not necessarily completely extinguish, hypertonia. The optimal dose should allow goal achievement without causing significant adverse effect. The dose can be adjusted every 24 hours, but this is not practical for all patients, who may not be able to visit the clinic more frequently than every few weeks. Thus, it may be several months of dose adjustments before the optimum dose is achieved.

The drug delivery mode needs to be modified to suit the patient's needs. In those with severe nocturnal spasms, but who are relatively symptom-free and functional in the daytime, the ITB pump can be programmed to deliver more baclofen at night, when more aggressive control of spastic hypertonia is desired, than in the daytime, when the patient relies on hypertonia for function. The ITB pump reservoir needs to be refilled with baclofen periodically. This typically occurs every 8–12 weeks, but it may be more frequent depending on the rate of daily drug infusion.

Rehabilitation management

ITB therapy is only one of the important components of the armamentarium of treatment of post-stroke spastic hypertonia. In order to achieve successful functional outcomes, ITB, just like any other spasmolytic intervention, should be used in conjunction with other treatment techniques, such as physiotherapy. This integrated approach will address not only spastic hypertonia, but also other associated movements such as weakness and incoordination (Table 2). Since ITB primarily affects the lower limbs, adequate spasticity control of the upper limbs may not be obtained unless other modalities, such as botulinum toxin or phenol injection, are employed.

In order to make the best use of resources, it is desirable that the ITB dose has been optimized, i.e., a certain degree of spasticity control has been achieved, and that the surgical wounds have healed, prior to commencing physical and occupational therapy. Although early mobilization is encouraged post-surgically, excessive movement, especially rotation and flexion of the trunk, should be restricted, in order to lessen the risk of catheter malfunction and pump malposition. When performing an evaluation after ITB placement, clinicians should view a patient as if he or she were new, since it is not uncommon after ITB therapy, different motor patterns and functional abilities could emerge. With tone improvement, latent movement pattern and postural control may be uncovered, and thus a patient's previous therapy program will need to be upgraded.

A team approach to spastic hypertonia management is preferred because the motor problems after a stroke are multiple. Physiotherapists play an important role in furthering the gains achieved from ITB therapy because even though spastic hypertonia has a neurologic basis, its significance is expressed in terms of physical limitations. Drug therapy deals with the ''positive'' signs and symptoms of the upper motor neuron syndrome, such as spastic hypertonia and agonist-antagonist muscle co-contraction. Pharmacologic treatment also frequently uncovers the negative symptoms, such as weakness and incoordination, which are not amenable to drugs, but to physical modalities that include stretching, strengthening, conditioning, and motor re-training. Because of the

Table 3. *ITB in post-stroke spastic hypertonia*

Study/Author	Subjects	Study design	Outcome
Meythaler *et al.* [19]	stroke = 3; TBI = 3	randomized, double-blind, placebo-controlled, cross-over (screening phase) 3 months follow-up	improved AS, SFS, and reflex scores no effect on motor strength on the normal side
Meythaler *et al.* [20]	stroke = 21	randomized, double-blind, placebo-controlled, cross-over (screening phase) 12 months follow-up	improved AS, SFS, and reflex scores no effect on motor strength on the normal side three subjects recovered ability to ambulate
Francisco and Boake [10]	stroke = 10, all ambulatory	open label mean 8.9 months follow-up	improved modified AS scores and gait speed. Preserved strength in unaffected limbs
Remy-Neris [23]	stroke = 4; TBI = 3	case series, open-label; bolus intrathecal baclofen only	improved AS scores and maximal walking speed, but preferred walking speed was unchanged minimal knee extension and maximal ankle flexion were the only kinematic data that significantly improved

UE Upper extremities, *LE* lower extremities, *FIM* functional independence measure, *ADL* activities of daily living, *AS* Ashworth scale, *SFS* Spasm frequency scale.

limitation in range of motion imposed by spasticity, short tissue shortening occurs. Thus, it is important to attempt to mobilize soft tissues and elongate the shortened structures through stretching and other modalities. Efforts to re-establish appropriate agonist and antagonist muscle relationship should also be exerted, since co-contraction of these muscles frequently occurs in spastic conditions. Strengthening of previously spastic muscles should also be considered because weakness of these muscles becomes more obvious after the excessive tone is controlled by ITB therapy.

Complications

Complications associated with ITB therapy can be grouped as patient-, operator-, drug- procedure- or system-related (Table 4). Patient-related problems include hypersensitivity to and intolerance of side effects of baclofen, and drug tolerance. Medication-related problems occur with drug under- or overdosing, typically secondary to error in pump programming. CSF leak, pump pocket seroma, and infection are common procedure-related complications. System-related complications are either due to the catheter (fracture, dislodgement, obstruction) or, rarely, the pump itself (malfunction or power failure). In extreme cases, when the pump fails, the catheter breaks or kinks, or when the pump is not refilled in a timely manner, baclofen withdrawal may occur, but this problem is manageable when detected early and intervention is delivered in a timely manner.

Table 4. *Complications of ITB*

Patient-related
– Hypersensitivity to baclofen
Drug-related
– Hypotension
– Dizziness
– Somnolence
– Headache
– Nausea
– Hypotonia
– Constipation
– Urinary retention
– Deep venous thrombosis
Pump manager-related
– Programming error
– Drug concentration error
– Incorrect entry of access port
Procedure-related
– CSF leak and spinal headache
– Pump pocket seroma
– Infection
Pump-related
– Flipping of pump (‘‘Twiddler’s syndrome’’)
– Overinfusion
– Underinfusion
– Stalled pump
Catheter-related
– Kink
– Fracture
– Occlusion
– Dislodgement

Timing of ITB therapy

In the United States, the Food and Drug Administration (FDA) approved the use of ITB for cerebral origin spasticity one year post-onset. In clinical practice, however, ITB has been used earlier based on the need to aggressively address severe and functionally-limiting spastic hypertonia. Early intervention is called for when other management methods are ineffectual or result in untoward effects, and when delay in treatment puts the patient at risk for complications.

Early use of ITB is controversial because baclofen, similar to other GABA agonists, has a potential negative effect on recovery [4, 11, 22]. A counter-argument, however, is that delayed spastic hypertonia intervention may be more deleterious because it may lead to complications and prevent functional recovery. Brunstromm [5] described six phases of motor recovery from stroke, commencing with flaccidity and culminating in return of normal, isolated movement. The middle stages are characterized by spasticity. Persons with stroke who have various degrees of spastic hypertonia and motor control may be considered as being trapped in the middle Brunstromm stages. Unless spastic hypertonia is controlled, they may not be able to progress through the more desirable later stages. Thus, at least in theory, early control of spastic hypertonia may have a facilitatory role on functional recovery.

Special issues in stroke

Anticoagulation

The use of anti-platelets and anticoagulants is common in persons with stroke. There is not enough evidence regarding the risk of withdrawing anti-platelets and anticoagulants prior to ITB screening or implant, thus is recommended that prior to withdrawing these medication prior to the screening trial and ITB implantation,

consultation with the appropriate specialists (cardiologists, hematologists, neurologists) be sought. Likewise, the medical and surgical teams must decide on the timing of anti-platelet and anticoagulation withdrawal and re-institution. A common clinical practice is switching from warfarin to low molecular weight heparin a few days prior to the procedure.

Bowel and bladder

Constipation is also commonly encountered in persons with stroke, either due to the effects of immobilization and debility or inadequate nutrition and hydration. Although changes in gastrointestinal motility following ITB implantation [16] have been reported, other conditions that cause constipation must be ruled out prior to adjusting ITB dose. The same is true for investigating urinary retention following ITB therapy. Certain premorbid conditions result in neurogenic bladder and bowel dysfunction, which may only be aggravated, but not caused, by ITB.

Catheter tip placement

Many clinicians believe that higher catheter tip placement will result in better effects on the upper limb [7]. However, there is no standard as yet regarding the optimum catheter tip location. Some argue that ITB dose, rather that catheter tip placement, is more crucial in achieving upper limb effects.

Sexual function

Post-stroke sexual function is less often addressed during recovery. While sexual dysfunction has been reported in the spinal cord injury group following ITB therapy [8], none has been reported in the stroke population. In the SCI population, ITB's effect on erectile dysfunction appears to be dose-dependent, since symptoms improved after decreasing ITB dose [8]. On the contrary, there have been anecdotal reports of improved sexual activity after successful tone reduction with ITB therapy that allowed better hygiene and positioning.

Weight gain

Another common observation following ITB therapy is weight gain. Most likely this results from the decreased caloric requirement following spasticity reduction. Thus, it is advisable to consider adjusting caloric intake once spasticity is adequately controlled. The issue of weight gain after ITB therapy is not unique to stroke survivors.

Seizures

Seizures, not related to ITB withdrawal, may occur after ITB therapy [15, 25], but the incidence in stroke is unknown. While the relationship between ITB therapy and seizures in multiple sclerosis has been established [23], its nature in stroke needs to be further clarified.

Endurance/fatigue

Following a stroke many patients complain of fatigue and decreased endurance, which limit performance of daily activities. When this occurs after ITB therapy, further investigation is warranted to determine the cause. Concomitant issues, such as weakness, depression, poor sleep, and side effects of medication – including baclofen – may result in fatigue. It is also possible that fatigue may be aggravated by increased activity that has become possible following satisfactory tone control.

Caregiver burden

Stroke has an impact not only on the patient, but as well as on the family and caregivers. A reasonable goal for ITB therapy is to decrease caregiver burden by allowing easier transfers and provision of care, and decreasing assistance needed once tone is adequately managed. However, it must be acknowledged that in certain situations caregiver burden may increase because of necessary clinic visits for ITB pump maintenance.

Conclusion

ITB is an important therapy for post-stroke spastic hypertonia. Unlike other modalities, such as oral medications, that have untoward effects including drowsiness, sedation, and loss of voluntary muscle power, ITB therapy has minimal adverse effect on arousal and cognition, and does not appear to weaken the uninvolved limbs. ITB should be considered when spastic hypertonia is severe enough to cause functional limitations and prevent progress in rehabilitation. In order to maximize functional benefits after controlling spastic hypertonia, ITB therapy should be applied in the setting of an integrated, multi-modality management approach.

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Intrathecal baclofen in the treatment of post-stroke central pain, dystonia, and persistent vegetative state

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Summary

Intrathecal baclofen (ITB) administration is a fully established treatment for severe spasticity. However, it is not widely known that baclofen, an agonist of the GABA-B receptor, has additional beneficial effects in other conditions such as chronic pain, coma, dystonia, tetanus, and hypothalamic storm. Sporadic cases of dramatic recovery from persistent vegetative state after intrathecal administration of baclofen have been reported. There have been also reports on the use of baclofen for control of dystonia due to cerebral palsy, neuropathic central pain syndrome or reflex sympathetic dystrophy. On the other hand, epidural spinal cord stimulation (SCS) has been used in the management not only of pain but also of spasticity, dystonia, and in order to improve deteriorated consciousness, but the effects so far have been modest and variable. Similarities between ITB and SCS are interesting as both involve the spinal GABAergic system. Based on a 15-year personal experience of intrathecal baclofen, I would stress the importance of this treatment not only for spasticity but also for other difficult neurological disorders.

Keywords: Intrathecal baclofen; pain; dystonia.

Historical introduction

It was more than 15 years ago when the first author became interested in the neurosurgical management of spasticity. At that time, no other neurosurgeon in Japan was involved in the neurosurgical management of spasticity. It was during my fellowship in Birmingham U.K. in 1988, when my great mentor, Professor Hitchcock, who used to perform stereotactic dentatotomy for various kinds of spasticity, introduced me to this field. Although the effect of dentatotomy was transient, I witnessed many cases of dramatic immediate relief from severe spasticity. This experience made me realize the importance of neurosurgery in the management of spasticity. At the time I returned to Japan, baclofen for intrathecal use was not available. I personally imported the medication from Basel, Switzerland, and started the trial bolus injections mainly to patients who had suffered cerebrovasular accidents. Implantable pumps for chronic treatment were also not available; however, even these bolus injections caused a variety of neurological changes which I noticed by doing careful clinical observation.

One day, in early 1990s, I injected intrathecally baclofen to a patient with foot spasticity after a stroke. The patient also had poststroke dysesthetic pain; to my big surprise, the patient reported not only relief from spasticity but also from the pain, which, initially, I could not believe. In the same room in the ward, there was another patient with poststroke central pain who had undergone thalamic deep brain stimulation and motor cortex stimulation without remarkable benefit. This patient eagerly asked me to offer him baclofen as a trial injection. I hesitated and explained the difference between these conditions and their indications, but the patient insisted on me trying, and finally I did it. Again, it worked equally well as it is shown in Fig. 1. I had not told the patient the expected time course of the drug effect, but the time curve of pain relief in him was compatible with the time curve of efficacy of bolus intrathecal baclofen for spasticity. Since then, I investigated the effect of bolus baclofen injection on various types of neuropathic pain.

The analgesic effect of baclofen is not widely known; however, baclofen is a second choice drug for idiopathic trigeminal neuralgia. In clinical studies, intrathecal baclofen relieves muscle spasm pain, an effect that is generally believed to be secondary to the relief of muscle spasm. However, there have been clinical reports on pain relief after intrathecal baclofen. Herman *et al.* [3] reported that central pain caused by spinal lesions is

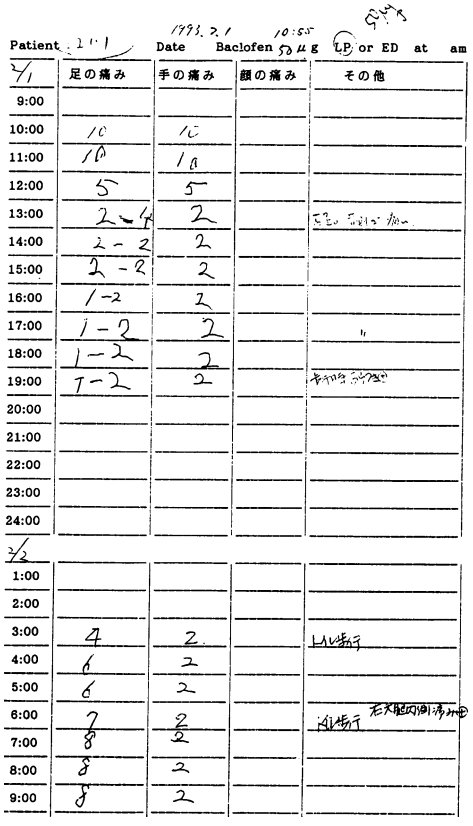

Fig. 1. Pain relief after intrathecal injection of baclofen. Baclofen was injected at 10:55 am; the pain in the leg became 2/10 after 4 hours; the effect on arm pain was still present on the following morning. Pain score was filled by the patient

successfully controlled with lumbar ITB and that, in his view, this was not a secondary result to systemic effects of baclofen. In their report, even a patient with a lesion high at the level of the third cervical vertebra (C3) experienced pain relief in the leg. I also reported that ITB suppresses poststroke central pain [5]. Similarly to patients with central pain of spinal origin, such baclofen analgesia can be explained by suppression of the abnormal neuronal activities in the spinal posterior horn. Baclofen analgesia is not mediated through the endogenous opiate system. The neural structures rostral to the medulla and caudal to the midbrain are necessary for the analgesic effect of baclofen. These findings suggest that there is an ascending pain control system from the spinal cord to the pons that is not associated with the opiate system. Baclofen acts on GABA-B receptor sites that are present in high concentration in the spinal dorsal horn, and therefore, GABA may be the mediator of this pain control system. It has been reported that GABA is released by electrical spinal cord stimulation [2, 4], a technique that has been used widely for pain relief. This further supports the importance of the GABAergic system in pain mechanisms [8].

In 1995, I was asked to accept a patient from the Kyushu area (900 km from Tokyo) for management of severe spasticity. The patient was a young boy who became unconscious and bed-ridden after a severe traumatic brain injury. I had no idea what to do. When I first saw him, he was severely tetraspastic, did not respond to verbal commands, and was thought to be in the so-called ''vegetative state''. Continuous infusion pumps for chronic intrathecal baclofen were not available and I desperately asked my residents to inject baclofen through a lumbar tap every day for at least one month. Then, to everyone's big surprise, the boy woke up after 25 injections, started talking, and eating by himself. Six months later, he returned home on foot (Fig. 2). At present, ten years later, he is a high school student. The recovery from the ''vegetative state'' was dramatic [7].

There are several communications that also describe the experience of dramatic recovery of consciousness in such patients after intrathecal baclofen. It is known that in children with cerebral palsy, selective dorsal rhizotomy and the resultant relief of leg spasticity may induce subsequent beneficial effects on higher brain functions. The effect of baclofen on persistent vegetative state may thus be secondary, but the effects in certain cases are so dramatic that we have to consider the primary role of baclofen on depressed consciousness. It is known that baclofen improves nerve conduction in demyelinated axons and therefore intrathecal baclofen may accelerate the repair of diffuse axonal injury. Spinal cord stimulation has been used in the hope of recovery from the persistent vegetative state, and in some cases, it is really effective. Thus, spinal cord stimulation and baclofen are also similar in terms of recovery from persistent vegetative state.

Spinal cord stimulation has been reported as an effective treatment for dystonia; however, the results were not consistent [10]. Intrathecal baclofen has been also introduced for the treatment of generalized dystonia due to either cerebral palsy or other conditions, and the results seem promising [1]. ITB represents a new therapeutic option for dystonia and reflex sympathetic dystrophy pain that is refractory to other treatments [9]. Spinal cord stimulation is regarded as the surgical treatment of choice for reflex sympathetic dystrophy. SCS increases cerebral blood flow by unknown mechanisms that are not related with increased sensory input. SCS has been tried in ischemic stroke or vasospasm after subarachnoid hemorrhage. To our knowledge, there is no clinical

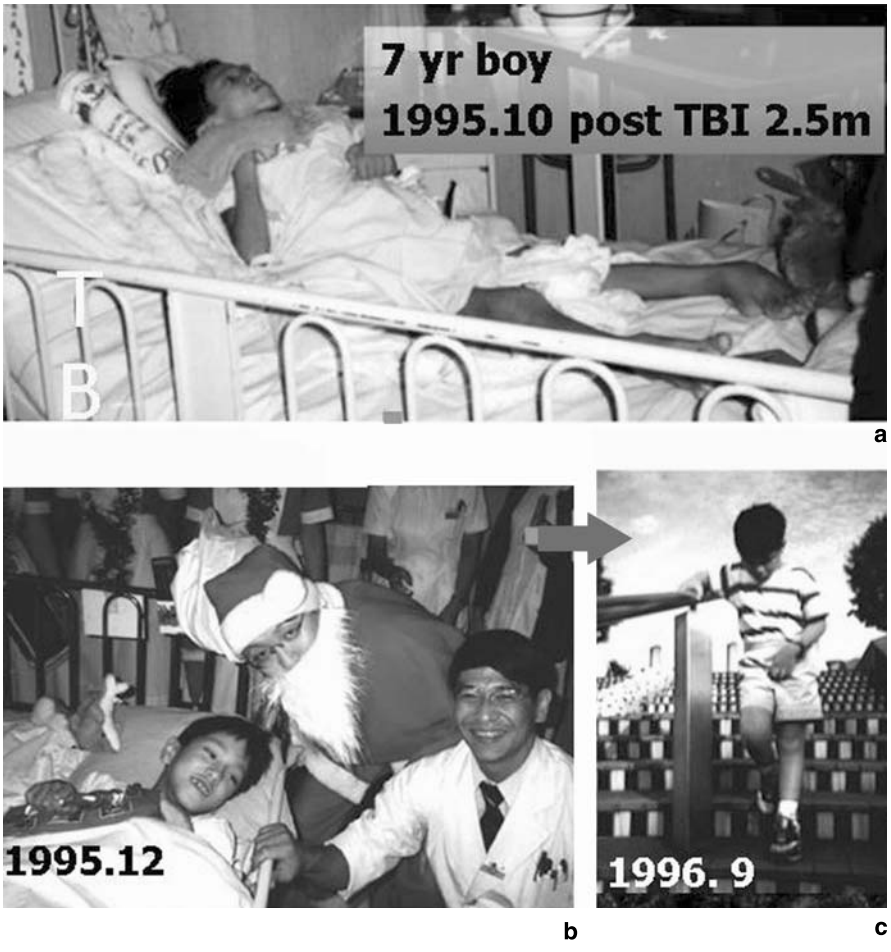

Fig. 2. Tetraspastic unconscious boy after traumatic brain injury (a). Intrathecal baclofen was used to relieve spasticity (b), and the level of consciousness improved dramatically (c)

report on the administration of baclofen and potential effects on cerebral blood flow (CBF). Experimental data, however, do show that CBF increases following intrathecal administration of baclofen.

ITB in Japan

In 2006, the Government of Japan finally approved intrathecal baclofen and implantable pumps after a 29 cases clinical trial. They had requested us to perform a high-cost domestic clinical trial despite the fact that several thousand patients have received the benefits of this treatment every year in many other countries. This delay which was caused by political considerations had the result that we learnt a lot more on the action of baclofen and the various aspects of intrathecal medical treatment.

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Neurophysiological basis and clinical applications of the H-reflex as an adjunct for evaluating response to intrathecal baclofen for spasticity

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Summary

Implanted programmable pumps that infuse intrathecal baclofen (ITB) markedly enhance the ability of clinicians to manage severe spasticity in appropriately selected patients. Studies addressing the efficacy of this treatment modality have primarily used clinical outcome measures of impairment, particularly reduction in stiffness as measured by the Ashworth scale. Several recent studies, however, highlight comparatively higher sensitivity of neurophysiologic techniques, especially the H-reflex, as an objective index of spinal cord response to ITB administration. We review the conceptual, physiological, and methodological bases for use of the H-reflex as an adjunct to clinical evaluation among patients receiving ITB infusion, including published reports and selected case studies that address the potential advantages and limitations of such techniques when applied to dose titration and system ''troubleshooting'' scenarios. We also address the implications of such findings in the context of reported complications such as ''tolerance'' to ITB administration and catheter ''microfracture.'' The accumulated knowledge suggests that H-reflex is a sensitive method for documenting altered spinal cord responsiveness in the presence of ITB delivery. We therefore recommend using H-reflex as an adjunct to clinical evaluation when judging the overall effectiveness of ITB administration.

Keywords: Baclofen; H-reflex; intrathecal drug infusion; spasticity; spinal cord; brain; injury.

Introduction

Continuous intrathecal baclofen (CITB) administration via the implanted programmable pump system yields potent, adjustable control of spastic hypertonia. CITB permits significant reduction of spastic hypertonia with serum baclofen concentrations far lower than when taken orally, thereby markedly reducing cognitive adverse effects. Following a successful screening trial, an externally-programmable pump is implanted into the abdominal wall and connected to a catheter that is inserted into the spinal canal, usually at the mid-to-lower thoracic vertebral levels. Baclofen is thus delivered directly into the cerebrospinal fluid at concentrations that progressively decrease from lumbar to cervical segments. The CITB dose is adjusted in an iterative procedure over several weeks or months following pump implantation to facilitate achievement of targeted functional goals. Extensive clinical experience exists with this form of treatment for spasticity of spinal and supraspinal origin.

Clinical measures of spasticity, such as the Ashworth scale and spasm frequency scale, form the basis for evaluating response to bolus or CITB administration in most settings. The value of these clinical scales, particularly the Ashworth scale, has been questioned with respect to validity and sensitivity [16, 20]. Further, clinical evaluation of resistance to passive stretch based on the Ashworth scale reflects passive, intrinsic, and reflex-mediated stiffness [8, 24]. Accordingly, it may be difficult to differentiate reflex-mediated stiffness, amenable to treatment with anti-spastic medication, from concomitant changes in the soft-tissues of the spastic extremity [18] when employing the Ashworth scale alone. Inclusion of objective and sensitive assessment techniques that complement the clinical examination may avoid limitations associated with exclusive use of clinical scales.

Laboratory techniques are becoming increasingly recognized as a means to objectively assess the effects of ITB administration. Ideally, such instruments are valid, reliable, sensitive, easy to perform, well tolerated, require little patient cooperation, and yield clinically meaningful information. In general agreement with early reports, recent studies confirmed that ITB reduces several biomechanical measures of spasticity, such as resistive

torque, joint stiffness, and stretch reflex responses, in a dose- and time-dependent manner consistent with clinical findings [3, 7, 21]. Techniques that evaluate changes in spinal cord excitability reflect the putative mechanism and site of baclofen action, that is, reduced release of excitatory neurotransmitters within the spinal cord. As baclofen significantly influences both mono- and polysynaptic reflexes, neurophysiological techniques such as the Hoffman (H)-reflex and flexion withdrawal reflex provide unique and complementary information regarding neurophysiologic response to ITB.

We recently proposed a conceptual framework for potentially useful applications of serial H-reflex recordings as an adjunct to clinical evaluation of response to ITB administration [29]. In this report, we review the neurophysiological and methodological bases of the H-reflex for monitoring CITB administration and provide evidence that substantiates some of the proposed applications for the H-reflex within this conceptual framework. Further, we present selected case reports that impart a unique and corroborative neurophysiologic perspective regarding selected problems reported in the literature among patients with the ITB pump, including catheter ''microfractures'' and ''tolerance.'' Finally, we discuss the advantages and limitations of this technique based on several years of experience.

Methodological considerations of the H-reflex for monitoring ITB administration

Protocol

The experience summarized here encompasses more than 700 recordings in nearly 100 prospective or current ITB pump recipients for management of spasticity of supraspinal (brain trauma, stroke), or less often, spinal origin. Prior to pump implant, each patient receives an ITB bolus injection as part of a screening protocol that includes assessments with clinical and neurophysiological measures. After pump implantation, patients are evaluated during routine outpatient visits that usually coincide with the time of pump refill and/or dose adjustment. The H-reflex is typically recorded prior to any dose manipulation, with the neurophysiologist being unaware of the programmed dose or mode of administration (e.g., simple or complex-continuous mode).

Recording technique

We record the H-reflex with the patient resting comfortably in the supine position, using 1-cm diameter surface Ag–AgCl electrodes placed 3 cm apart and midline along the belly of the soleus muscle after the skin is slightly abraded to reduce the impedance. Stimulating electrodes are placed in the popliteal fossa (cathode, round, 3 cm in diameter) and above the knee cap (anode, square, 4.3×3.7 cm). The amplifier filters are set from 2 Hz to 5 kHz. The H-reflex is evoked using 1-ms pulses repeated every 10 s. Stimulus repetition frequencies higher than 0.1 Hz are not recommended as they may reduce the size of the response due to post-activation (homosynaptic) depression. Auditory feedback is provided to eliminate muscle activation during the recording, as much of the variability in the H reflex amplitude observed during repeated trials is due to changes in the level of activation of the motoneuron pool. We increase stimulus intensity in small increments (0.8–1.6 mA), from threshold for H-reflex to supramaximal for M wave, and record 20–30 traces, one at each intensity. Thereby, a bell-shaped H-reflex curve and a sigmoid M-wave curve are mapped with special attention to the H-reflex ascending limb and the peak, which should be smooth. With our technique, variability of responses is rather small. With less cooperative subjects, several trials may need to be averaged at each intensity. Bilateral recording typically takes about 30 minutes including the set-up.

Amplitudes of the maximal H-reflex and maximal M wave are measured. The neurophysiological outcome measure is the H/M ratio (%), the amplitude ratio between the maximal H-reflex and the maximal M-wave. Expressing the size of the H-reflex relative to the M wave limits the influence of confounding factors that may affect the absolute amplitudes of responses recorded on repeated sessions over an extended period of time, e.g., skin impedance, relative positions of the recording and stimulating electrodes with respect to orientation of muscle and nerve fibers, thickness of subcutaneous tissue, or muscle mass. The H/M ratio indicates the proportion of the motor neuron pool activated by synchronous Ia afferent input. By controlling experimental conditions through the M wave, changes in the H-reflex amplitude and therefore, the H/M ratio, reflect alterations in the excitability within the mono/oligosynaptic reflex network. The physiologic basis and limitations of the H-reflex have recently been reviewed [15].

Reliability of the H/M ratio

Establishing the reliability of an outcome measure is critical before basing clinical decisions on the information it is believed to provide. For the purpose of monitoring

the changes in spinal reflex excitability with CITB, it is necessary to appreciate the degree to which the size of the H/M ratio varies from session-to-session as well as its sensitivity to detect changes that follow CITB infusion. In other words, the within-person variability over time should be small in comparison to the magnitude of H/M changes that accompany typical adjustments in the CITB dose. There are few studies specifically addressing the repeatability of the H/M ratio. Levin and Hui-Chan [11] measured H/M ratio in 9 chronic ambulatory stroke patients on 3 occasions, each a week apart. They reported an intra-class correlation coefficient (ICC) of 0.94, which indicates a high stability of H/M over time. Comparable ICC (0.85) was reported among healthy subjects studied on several occasions [4]. The results of these investigations suggest that H/M ratio may be used to assess interventions over several days or weeks.

Retrospective review of our subjects studied twice before pump implantation provides an opportunity to assess the reproducibility of our technique. We identified 11 subjects with 18 recordings performed on two occasions, on average 214 days apart (range 1 day to 3.5 years). The results are presented in Fig. 1, where different symbols denote different time intervals between the two studies. On inspection, the data points appear narrowly scattered above and below the line representing a perfect agreement between results of the two recordings, consistent with a high degree of repeatability. There is a single clear outlier (circled) and this data point belongs to a subject seen 3.5 years after initial evaluation. The H/M ratios measured on the opposite side differed by only 2% from the first recording, suggesting that factors

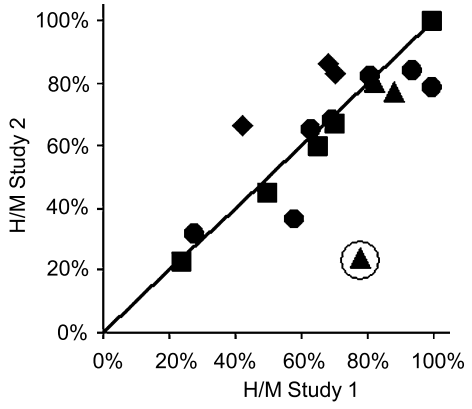

Fig. 1. Repeatability of H/M ratios from 18 recordings in 11 subjects. Symbols denote time elapsed between the two studies: 1–5 days (circles), 3–4 weeks (diamonds), 5–6 months (squares), and 2–3.5 years (triangles). The line indicates a perfect agreement between the two recordings. Inclusion/exclusion of the outlier (circled) did not significantly alter the results

other than recording methodology are likely to be responsible for the difference. Further, it is apparent that the time interval between the two recordings does not seem to affect the variability of the H/M ratio.

We formally assessed test-retest repeatability using different parameters [13], with an outlier excluded. The ICC calculated based on the two-way ANOVA was 0.86, consistent with previously cited studies. The difference (mean $\pm$ SD) between the two recordings, expressed as an absolute value, was $8 \pm 8\%$ (range 0–24%), with the corresponding 95% confidence interval of 4–12%. The actual difference between the second and first recordings was $-1 \pm 12\%$, with the confidence interval ranging from -7 to 5%. A mean inter-recording difference near zero, coupled with a confidence interval that includes zero, confirms the absence of systematic bias in the H/M ratio with repeated evaluations. This was further verified using a Bland-Altman plot, where the difference between each pair of data points is plotted as a function of their mean. The plot indicated a random rather than systematic change in the H/M ratio across the entire range of data points. The coefficient of variation of H/M ratio for the two recordings combined was 13%. Multiplying it by the overall mean H/M ratio in this sample (67%) yields 9% as the typical variation of the mean H/M ratio from one session to the other. For practical purposes, we consider a change in H/M ratio of 10% or below to be within a range of methodological and biological variability that prevents us from making valid inferences about changes in spinal reflex excitability with ITB administration. Conversely, we deem H/M changes in excess of 10% to indicate evidence of an actual difference in spinal reflex excitability. In our experience, ITB dose titration adjustments of 10–20% (e.g., 100–120 mcg/day) early after pump implantation result in H/M ratio changes that considerably exceed the 10% criterion. We conclude that the H/M ratio is a reliable indicator of changes in spinal reflex excitability in the presence of ITB infusion.

H-reflex and ITB bolus administration

An ITB bolus significantly reduces the H/M ratio in a dose- and time-dependent fashion [2, 9]. H/M ratio progressively decreases within minutes of bolus administration [10] and remains significantly decreased or virtually absent from one to several hours thereafter in both children and adults [5, 19]. When compared with Ashworth score after an ITB bolus, the temporal profile of H/M ratio change precedes the peak and persists beyond the

duration of apparent Ashworth score change. We recently confirmed that the H/M ratio is more sensitive than the Ashworth score or F-wave in detecting a physiological response to a 50-mcg ITB bolus among 30 adults with severe-to-moderate spasticity after acquired brain injury [26]. In most subjects, the H/M ratio was below 20% and often absent at ~5 hours after the injection. Soleus H/M ratio was the most sensitive measure of physiological drug action, regardless of the degree of initial muscle hypertonia or initial H/M ratio. Accordingly, we proposed that the H-reflex is useful for verification of ITB bolus administration, particularly when clinical findings are equivocal, such as among patients with moderate spasticity at rest or with small changes in Ashworth score. The enhanced sensitivity of the H/M ratio to ITB bolus injections, when compared with the Ashworth score, established a basis for employing the H-reflex technique for physiological monitoring of CITB administration after pump implantation, as previously suggested [10, 14].

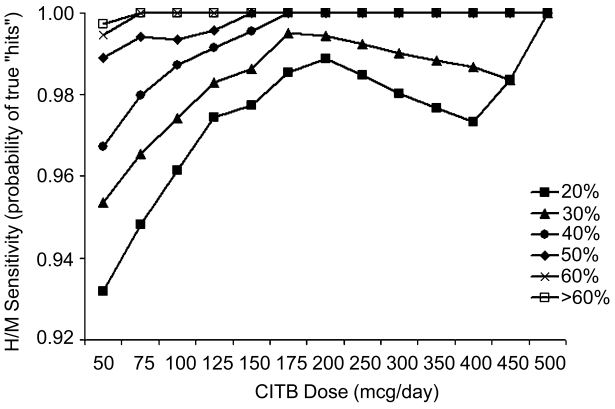

Fig. 2. Sensitivity of the H/M ratios of different sizes (20–60%) across various CITB doses. Sensitivity is calculated as the probability that the H/M ratio is equal to or smaller than a given size if CITB delivery is equal to or larger than a given dose. Note overall greater sensitivity of larger H/M ratios across all ITB doses. This indicates that if the system is functioning H/M ratio is expected to be no more than 20% across the range of CITB doses

H-reflex and CITB administration

Anecdotal observations of clinical spasticity reduction among recipients of the ITB pump suggest that response to a specific daily dose of CITB shows greater variability than that of a one-time 50-mcg bolus. For example, some patients will respond briskly to a modest dose of 100 mcg/day, whereas others will require titration beyond 300 mcg/day for comparable reduction in muscle hypertonia. Moreover, our clinical experience with concurrent neurophysiological monitoring of ITB pump recipients indicates that H/M ratio reaches a plateau or completely disappears at doses that are lower than that required for "optimal" management of spastic hypertonia. In other words, titration of CITB dose often proceeds beyond the point at which H/M ratio levels off.

Exploration of the clinical implications of a discrepancy between clinical and neurophysiological responses to CITB administration requires a greater level of understanding of typical dose-response behavior. Thus, we recently reviewed over 200 H-reflex recordings in more than 30 subjects with no known pump problems. We examined H/M ratio changes as a function of CITB dose, combining data from each leg. Consistent with our expectations, we observed a sharp initial decline in H/M ratio from baseline that soon reached a plateau with increasing CITB dose. We first dichotomized data using different cutoff points for the H/M ratio (10–80%) and the CITB dose (50–500 mcg/day), and then calculated H/M sensitivity, employing a methodology used in a recent study aiming to define optimal cutoff points for clinical outcomes in acute stroke [28]. Based on this approach, H/M sensitivity indicates the probability that the H/M ratio is equal to or smaller than a given size if CITB administration is equal to or larger than a given dose. Figure 2 shows the probabilities for different H/M ratios (20–60%) across the range of CITB doses. All probabilities exceed 0.90 and are somewhat smaller for smaller H/M cutoff points and lower CITB doses. The values approach 1.0 starting with the H/M ratios of 30% and above at CITB doses of 275 mcg/day and larger, reaching 1.0 for H/M ratios of 60% and above across all CITB doses. These findings imply that H/M ratios are expected to be no more than 20% at moderate and high CITB doses. The overall results suggest high sensitivity of H/M ratio to CITB administration.

We expanded upon these observations and derived CITB "effective doses", that is, the CITB doses at which the baseline H/M ratio, recorded in absence of baclofen, is expected to be reduced to 75, 50, and 25% of the control value. The estimated "effective doses" were 30, 70, and 110 mcg/day, on average [27]. In the same report, we presented evidence that a two-decay exponential function yields a curve that best describes the relationship between the H/M ratio and CITB dose. We further reported odds ratios for three H/M cutoff points across three CITB doses based on logistic regression analysis. The results indicate, for example, that if a CITB dose is above 150 mcg/day, the H/M ratio is about 13 times more likely to be below 10%, 36 times more likely to be below 20%, and 86 times more likely to be below 40%.

These results statistically confirm the marked sensitivity of the H/M ratio to CITB and have potentially important implications for clinical management of patients with implanted pumps, as discussed below.

Implications for clinical management of patients with ITB pump

Depression of the H-reflex has been considered a marker of the antispastic effect of baclofen, reflecting its influence on the GABA-ergic mechanisms involved in depression of spinal reflex excitability [19]. In 1989, MacDonell *et al.* [14] were among the first to propose that the H-reflex (H/M ratio) may be useful in establishing optimum dosage for ITB administration. Sallerin-Caute *et al.* similarly suggested measurement of the H-reflex to gauge the effectiveness of ITB [22]. However, these suggestions, until recently, did not find broader clinical application.

The evidence reviewed thus far presents a solid methodological and physiological foundation for predicting H/M ratio response to ITB administration. It also provides a basis for anticipation of H/M ratio behavior in clinical scenarios with suspected problems in ITB delivery. Since interruption of ITB administration occurs in a minority of patients with long-term use, few subjects are available to serve as ''proofs of concept'' for specific types of problems. Combining our early experience among patients with and without problems, we proposed several clinical scenarios where H-reflex may be useful [29], providing it is serially recorded beginning with baseline evaluation (Table 1).

During the ITB bolus trial, the H-reflex may serve as an objective confirmation of the physiological response to ITB administration. This may particularly be useful in clinically challenging situations, such as when considering placebo response due to difficulty with drug injection, if resting hypertonia is moderate, in the presence of stiffness of non-reflex origin (contracture), or whenever changes in clinical stiffness measures are modest or ambiguous. We place considerable importance to changes in H/M ratio early after the pump implantation, as it is more sensitive than clinical measures at lower CITB doses. Almost without exception, we see no clinical change prior to decline in the H/M ratio. It is our experience, therefore, that changes in H/M ratio often herald and precede a CITB dose when clinical response is about to be observed. Consequently, if the H/M decreases at a somewhat slower rate than predicted, it may be justified to increase the CITB dose in larger steps at first, followed by a more gradual adjustment in anticipation of the desired clinical response. Thus, we use the H/M ratio as an early marker of pharmacological response that permits us to accelerate the initial dose increments. As the H/M ratio approaches a nadir, we direct our attention more toward clinical assessment and functional goals set forth prior to pump implantation for arriving at the optimal CITB dose.

A lack of steady decline in the H/M ratio despite CITB aggressive dose increases should raise a suspicion of a possible ''early system malfunction''. Furthermore, once the optimal clinical dose is established, an increase in the H/M ratio from the nadir should raise a suspicion of inadequate CITB delivery. A progressive or an abrupt increase in the H/M ratio despite aggressive CITB dose increases (''paradoxical response''), particularly with an apparent loss of clinical response, should alert the clinician to the possibility of a ''late system malfunction''.

Table 1. *Proposed applications of H-reflex serial recordings as an adjunct to clinical management of ITB administration*

Troubleshooting application	Clinical presentation (if problem present)	H/M response (if problem present)
Confirmation of (un)successful bolus administration	1. lack of pronounced change in stiffness (i.e., Ashworth score) or 2. subjectively apparent clinical response (placebo)	(in)significant change from baseline
''Low reservoir syndrome''	symptoms of increased spasticity and/or apparent ITB withdrawal when pump reservoir volume is low	markedly increased H/M ratio compared with prior measurements at the same dose; reverts to prior range shortly after pump refill
''Late'' system malfunction	symptoms of increased spasticity and/or apparent ITB withdrawal independent of pump reservoir volume	markedly increased H/M ratio compared with prior measurements at the same dose; does not revert to prior range after significantly increasing dose or programming supplemental boluses.
''Early'' system malfunction	no clinical response despite upward dose titration often without history of symptoms suggestive of ITB withdrawal	insignificant change from baseline despite significantly increasing dose or programming supplemental boluses.

Thus, concurrent changes in H/M ratio and clinical response should raise a suspicion of possible system malfunction and prompt further evaluation. Serial H-reflex recordings may also be employed as a part of the troubleshooting protocol. As in the case of a screening bolus trial, the H/M ratio is more likely to detect a response to test boluses programmed through the pump than clinical measures alone. Accordingly, we routinely record H-reflexes along with clinical and imaging assessments for evaluating the status of the ITB system. Our experience leads us to believe that, due to its high sensitivity, H-reflex may suggest a problem even in the absence of visible interruption on imaging techniques. Thus, the H-reflex has a complementary role in the troubleshooting protocol. Some of the described applications will be more apparent when presented in the context of case presentations below.

Partial interruption of CITB delivery

Recent reports point to the existence of cases where CITB delivery is incompletely interrupted [6, 23]. This may take the form of a lasting ''partial'' compromise of drug administration (e.g., ''microfracture''), or as a transitional state that ultimately results in complete loss of flow through the catheter. A partial loss of previously effective response may prompt more aggressive dose increases, switching to other modes of administration (e.g., complex-continuous, multiple bolus), and even mixture of intrathecal morphine or clonidine to circumvent presumed ''tolerance'' to CITB. In cases of partial interruption of CITB delivery, the clinical presentations are variable and often confound early diagnostic interventions [23]. Unlike previously described situations in which CITB delivery is completely compromised and H/M ratio approaches pre-ITB levels, prediction of concurrent clinical and neurophysiological response is not straightforward. As will be described below, H-reflex evaluation provides unique and corroborative evidence for the existence of such incomplete CITB delivery problems. Moreover, based on the accumulated clinical and neurophysiologic evidence, we believe that these problems may be more prevalent than the small number of published case reports would suggest.

In 2003, Dawes and colleagues [6] described the case of an 8-year-old boy with an implanted ITB pump who presented with intermittent signs of baclofen under- and overdose. Pump interrogation, measurement of residual reservoir volumes, plain X-rays, intrathecal catheter contrast fluoroscopy, and CT scan of the intrathecal catheter tip were all unremarkable. Confirmation of a problem only occurred after revision of the catheter, which was later examined under light and scanning electron microscopy and revealed the presence of a microfracture. Symptoms resolved following replacement, interestingly, at a dose considerably lower than prior to catheter revision. The salient features of this case graphically confirmed that microscopic fractures exist in some ITB catheter systems. These could present with vague or intermittent symptoms that confound detection with conventional imaging techniques employed in troubleshooting scenarios. Importantly, the case demonstrates that a microfracture could cause smaller CITB delivery than the dose supposedly administered through the ITB system.

H/M ratio in partial interruption of CITB delivery

We know of no publications that report neurophysiological findings associated with a *confirmed* catheter malfunction resulting in *partial* delivery of programmed CITB dose. Extrapolation from patients with and without suspected problems prompts us to postulate that such cases would potentially demonstrate one or more of the following findings on serial H-reflex evaluations (in order of progressively *greater* flow interruption):

1. Low H/M ratio (i.e., continued ''suppression'') during simple continuous mode of administration with suboptimal clinical relief of hypertonia following previously satisfactory clinical response. Due to its high sensitivity, the H/M ratio may remain suppressed if sufficient CITB is present to reach target receptors, even though higher doses may be needed to achieve clinical response. Thus, higher CITB doses with small catheter leaks can theoretically result in suboptimal clinical response without apparent neurophysiological change.
2. New-onset of variable H/M ratios (''see-saw'' pattern) with simple continuous administration after a period of consistently lower values, with or without changes in hypertonia, depending upon the persistence of intermittent dose interruption.
3. Programmed bolus of $\geq$50 mcg yields appreciable decrease in H/M ratio, and possibly hypertonia, but return to simple continuous mode leads to variable or increased H/M ratios and hypertonia.
4. Progressive or abrupt increase in H/M ratio and hypertonia to pre-ITB levels with simple continuous or programmed bolus administration, i.e., evidence of complete loss of CITB delivery.

These postulated neurophysiological findings reflect varying degrees of discrepancy between the programmed and actually delivered CITB doses. The proposed framework also highlights that H/M ratio is used in conjunction with, and *not* instead of clinical measures of spasticity. Rather, H/M ratio is employed as a sensitive index of CITB delivery by assessing changes in spinal reflex excitability at doses or increments not sufficiently high to appreciate clinical change.

Case presentation of partial/progressive interruption of CITB delivery

A 27-year old man with a history of ischemic stroke one year earlier presented to our spasticity and related motor disorders clinic with unilateral weakness and increased tone in the right upper and lower extremities. Treatment included oral baclofen, physical therapy, orthoses, and botulinum toxin injections. Sedation with higher doses of oral antispasticity agents and evidence of some preservation of underlying motor control prompted consideration of an ITB bolus trial. He responded favorably to a 50-mcg ITB bolus, with improved mobility, and proceeded with pump implantation. The CITB dose was progressively increased over the next four months with reduction in H/M ratio and hypertonia. At 210 mcg/day, the H/M ratio was noted to be increased; continued suboptimal clinical response prompted a dose increase to 250 mcg/day. Within a few days of the dose change, the patient complained of urinary retention. This was attributed to the higher CITB dose, prompting a decrease to 240 mcg/day. On two evaluations a week apart at 240 mcg/day, however, the H/M ratio kept increasing, particularly on the right side (Fig. 3). Concurrently, urinary retention persisted, tendon taps became more hyperreflexic, and Ashworth scores increased in the upper extremities. The patient denied itching and motor restlessness, and was not in distress. Given the lack of evidence of abrupt withdrawal, we considered the possibility that some CITB was still flowing and reaching

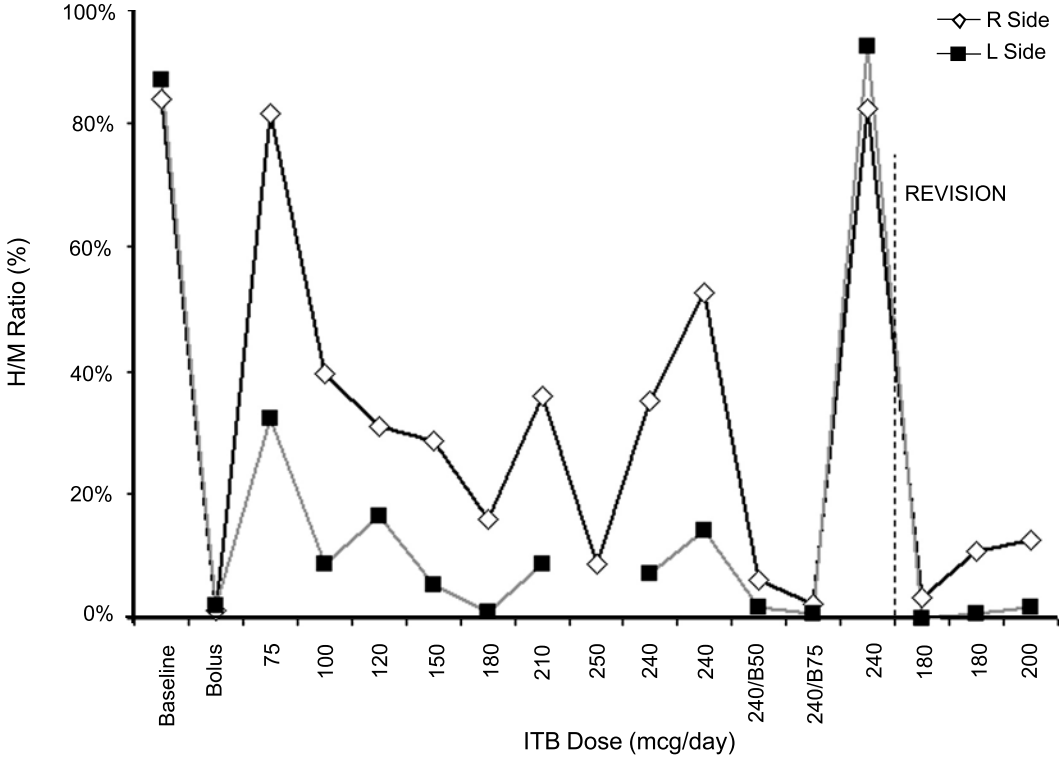

Fig. 3. Changes in the right (open diamonds) and left (filled squares) H/M ratios at various ITB doses acquired in a stroke patient over a one-year period. Several distinct features of the H/M ratio are present: 1) pronounced response at 5 hours after a 50-mcg screening bolus trail 6 months before the pump implantation (Baseline-Bolus), 2) typical dose-response decrease after the pump implantation (75–180 mcg/day), 3) variable and progressively higher H/M ratios (210–240 mcg/day), raising a suspicion of partial interruption of CITB flow, 4) decreased H/M ratios at 4 hours after 50- and 75-mcg programmed boluses (240/B50–240/B75), suggesting somewhat preserved flow through the catheter, 5) rebound to baseline levels at 240 mcg/day, indicating complete interruption of CITB flow, 6) nearly complete absence of the H/M ratios at smaller CITB doses than prior to the revision (180–200 mcg/day) with the size close to that just prior to the onset of variable responses (180 mcg/day). Note similar pattern between the two sides

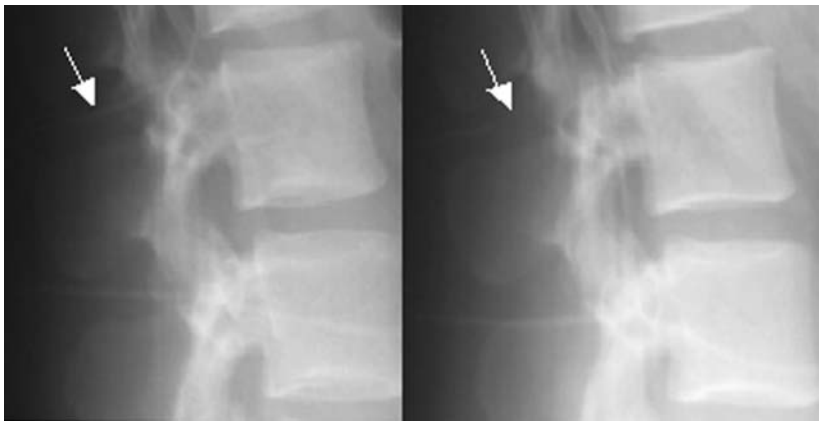

Fig. 4. Lumbar radiographs of the patient shown on Fig. 3. Left panel shows intact catheter immediately after the pump implantation. The arrow on the right panel points to catheter discontinuity revealed prior to the pump revision

the spinal cord. We therefore programmed two boluses, 50 mcg and 75 mcg several hours apart, to test whether bolus administration could support evidence of catheter integrity. Both resulted in pronounced decreases in H/M ratios and patellar muscle stretch reflexes. Urological symptoms initially seemed slightly improved, but then returned upon cessation of the perceived effect of the bolus administration, with further increase in H/M ratio that now closely approximated baseline values. These findings indicated persistence of some problem with ITB delivery. Figure 4 (right panel) shows a lumbar radiograph obtained within 24 h of the second bolus with a fractured catheter and a $\geq$2 cm gap between the ends of the catheter, in comparison to a baseline radiograph obtained one week after implantation (left panel). After catheter revision, urological symptoms resolved and hypertonia decreased. At the same time, H/M ratios at 180 mcg/day were similar to those recorded at the same CITB dose during the initial titration period.

This case graphically illustrates some of the clinical and neurophysiological findings associated with partial and progressive interruption of CITB delivery. Evidence of a catheter-related problem included new clinical symptoms (urological) with preceding variable H/M ratios.

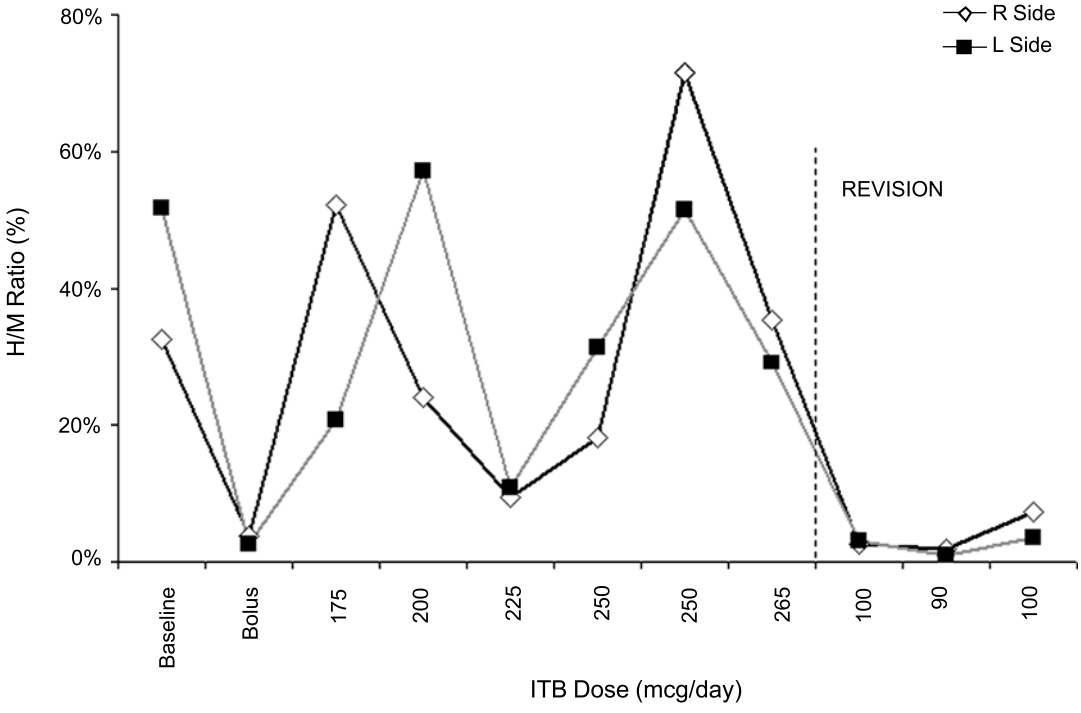

Fig. 5. Variable H/M ratios during dose titration in a patient with history of spinal stenosis and recent ITB pump implantation. Clinical response never approaches that observed during the bolus trial, and H/M ratios often rebound to baseline level throughout despite dose increase. Marked clinical improvement and typical H/M profile at low CITB doses follow catheter revision

In this case, we believe that a programmed bolus succeeded in delivering sufficient CITB to suppress the H/M ratio, presumably through a fibrous sheath surrounding the fractured catheter, whereas the simple continuous mode of administration was unable to do so. The problem progressed until remedied by surgical revision of the catheter, followed by satisfactory clinical and neurophysiological responses. Retrospective review of the neurophysiological profiles of our patients requiring catheter revision has demonstrated some with variable H/M ratios (Fig. 5). We postulate that partial catheter interruption may yield intermittent periods of ''effective'' or near-normal CITB delivery, perhaps influenced by changes in patient position, resulting in variably suppressed H/M ratios and a general absence of severe withdrawal symptoms. In summary, we believe that the variable H/M ratios on serial recordings represent a marker of partial interruption of CITB delivery, that otherwise may remain undetected until complete loss of flow.

Implications for suspected CITB "tolerance"

Postsynaptic neuronal activity is continuously regulated in terms of the number of receptor sites and the threshold required to generate a response. Both are negatively influenced by the concentration of agonist to which the target neuron is exposed. Thus, chronic exposure to excessive concentrations of an agonist can lead to adaptive changes in receptors so that response to a given concentration of the drug is reduced, i.e., *tolerance*. Cerebrospinal fluid baclofen concentration, diffusion, and receptor distribution in the spinal cord bear particular relevance to the discussion of physiological sensitivity and causes of response loss (e.g., catheter microfracture) among patients with CITB administration.

Presumed pharmacodynamic tolerance has been implicated as a cause of acquired loss of clinical response to CITB [1, 25, 17]. Closer examination of studies and case reports of CITB ''tolerance'', however, suggests that the reported clinical findings may not reflect the same underlying physiological phenomenon. Studies of tolerance that involve patient cohorts receiving CITB for spinal spasticity address time-dose relationships, and conclude that tolerance accounts for some of the observed dose increases during the first year after pump implantation, but not afterward [1]. These patients responded to CITB, albeit at a higher dose than that noted soon after implantation [1, 17]. In contrast, case reports of tolerance usually describe individual patients without apparent response to very high CITB doses (typically >1000 mcg/day). Some cite negative catheter contrast fluoroscopy results as evidence that no system malfunction is present, thereby ascribing the lack of clinical response to ''tolerance'' [25]. While the limited H/M ratio data suggestive of partial CITB delivery certainly do not refute the existence of CITB tolerance, perhaps revisiting the tolerance issue is warranted. Based on documented evidence of subdural catheter migration [12] and microfractures in particular [6, 23], we believe that some of the cases of CITB ''tolerance'' may represent unrecognized partial catheter malfunctions.

Limitations of the H-reflex for monitoring CITB administration

Several limitations warrant consideration when applying the H-reflex among patients with the ITB pump. First, we emphasize that the H-reflex (H/M ratio) is not being used as a measure of spasticity *per se*, but as an index of spinal cord responsiveness to CITB administration. Second and most importantly, it is being used as an adjunct to the clinical examination, specifically evaluating changes in the monosynaptic reflex arc due to baclofen. While the H/M ratio is more sensitive than clinical assessment at lower CITB doses, and is not susceptible to the confounding influence of soft tissue changes, we maintain that this measure should not be considered a ''stand-alone'' diagnostic intervention. Third, isolated H-reflex recordings are of limited value; the greatest utility is seen when prior measurements are available for comparison purposes, preferably including the pre-ITB baseline and bolus trial results.

Methodological and technical issues comprise the remaining caveats regarding the potential utility of the H-reflex for monitoring ITB delivery. Among the nearly 100 patients evaluated thus far, we have measured some with baseline H/M ratios that are very low, i.e., $\leq$15–20%. Thus, while H/M ratios are often increased in the presence of hypertonia, this is not always the case. In such patients, pre- to post-implant comparisons are less intuitive, considering the limited range for the H/M ratio change.

Children may have difficulty tolerating the procedure as supramaximal stimulation is needed for determination of the maximal M-wave amplitude. This has prompted some to limit the recording to the maximal H-reflex amplitude. We believe that this approach compromises the sensitivity of this technique. It is conceivable that extreme changes in the H-reflex amplitudes (e.g., from low/absent to high) may be meaningfully interpreted in

the clinical context of an abrupt system malfunction. However, lesser changes in the H-reflex amplitude remain ambiguous. For example, modestly oscillating H-reflex amplitudes may represent a variable response due to partial interruption of CITB delivery, or the inherent variability proportional to the M wave changes, with a resulting stable H/M ratio. Furthermore, when we re-examined our reproducibility data, the coefficient of variation of the H-reflex amplitude was nearly three-fold higher (34%) than that for the H/M ratio (12%). With the mean H-reflex amplitude of 7.4 mV in that sample, the corresponding variation of the H-reflex from session to session could be as high as 2.5 mV. Such a variability is quite high and, in our opinion, significantly limits the sensitivity and utility of this parameter.

Lastly, the need for electrophysiological equipment, skilled operator, and time may also be perceived as limitations. We believe, however, that the majority of settings appropriate for evaluating and managing patients with the ITB pump will have access to basic electrodiagnostic equipment and clinicians familiar with the technique. The procedure takes approximately 30 minutes to perform, including set-up. In our experience, patients are motivated to participate and invest their time after understanding the potential benefits. Regular recordings are recommended during the early dose titration phase after pump implantation. As the CITB dose increases and the H/M ratio reaches its steady-state nadir, however, neurophysiological assessment may be reserved for suspected suboptimal response, i.e., troubleshooting scenarios.

Conclusion

Neurophysiological recordings provide the clinician with objective, reproducible, and sensitive information regarding the central nervous system response to ITB administration. Such information should be viewed as complimentary to the clinical evaluation. H-reflex is useful for verification of ITB bolus administration, particularly among patients with moderate spasticity at rest or with small changes in hypertonia. Serial H-reflex recordings provide information regarding the dose-response relationship between the H/M ratio and CITB dose, that may aid dose titration after pump implantation. Furthermore, the accumulated evidence suggests that the marked sensitivity of the H-reflex may also prove advantageous in other clinically challenging situations, such as early identification and characterization of ITB system problems.

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The importance of neurorehabilitation to the outcome of neuromodulation in spasticity

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Summary

The neuromodulation specialist who is involved in the management of spasticity should not be interested only in the technical aspects of the implantation of a device. It is important that (s)he has a sound understanding of all aspects of this serious disability in order to determine appropriately whether an ablative or a neuromodulatory intervention (intrathecal baclofen administration, spinal cord stimulation, peripheral nerve stimulation) is best for the patient. It is also important that s(he) is able to collaborate effectively with the physiatrists, othopaedic surgeons, neurologists, physiotherapists, neuropsychologists, and care counselors. In this article, we review our approach to the neurorehabilitation of patients with spasticity due to multiple sclerosis, spinal cord injury, cerebrovascular disease or head injury and, on the basis of our experience, we highlight the importance of the integrated management that combines both rehabilitation and neuromodulation methods in order to ensure the maximum benefits for the patients.

Keywords: Spasticity; hypertonia; rehabilitation; neuromodulation; spinal cord lesion; baclofen; pump; rehabilitation.

Introduction

The treatment of spasticity is part of an integrated therapeutic approach, which takes into account the serial clinical evaluation of the patient, the stage of the underlying disease, the location of the lesion (brain or spinal cord), the severity of the damage (complete versus incomplete), the coexisting neurological or systemic problems, and finally, the short- and long-term aims of the neurorehabilitation program. It is important that the following questions are answered before the beginning of a treatment program [48]: a) Is treatment necessary? b) Which are the aims of treatment? c) Does the patient and caregivers have enough time to follow the selected therapeutic program? and d) Will the treatment interrupt patient's and care-giver's daily activities?

The best time for the commencement of management of spasticity is the stage when the clinical picture has been developed sufficiently and problems related to the functional capabilities of the patient start to present. When spasticity has been established, muscle shortening leads gradually to muscle contractures and ankylosis [13]. Our interventions should aim to prevent subsequent contractures of the affected muscles and to prepare the patients for active participation in the rehabilitation program. The management of spasticity begins at the stage of loose paralysis and aims to the maintenance of full range of joint motion, elasticity of soft tissue and muscle compliance (elasticity) [34]. It is important to avoid tendon loosening in paralyzed joints (e.g. in the shoulder of a hemiplegic arm) because this may lead to subluxation; such complications are difficult to treat and cause more functional problems than spasticity itself. It is known that, in addition to absolute muscle length, the length and position of a muscle relative to its adjacent tissues also determine the active and passive force that the muscle exerts at a particular tendon [43]. During the period of loose paralysis, cautious positioning of the body and affected limbs is mandatory for facilitating patient's entry to later stages of the neurorehabilitation program. For example, when the patient reclines, the limbs should be kept in positions opposite to those expected when spasticity will develop. Similarly, when the patient is on the wheel-chair, the head and upper torso should be supported by appropriate braces, while suitable ankle orthoses will keep the feet in slight dorsiflexion.

During the stage of spasticity, the position of the head and body affects directly or indirectly the level

Table 1. *Clinical findings in spastic paralysis of cerebral origin*

Disorders of neuromuscular control
– Poor control of head and body movements
– Abnormal postures
Abnormal muscle tone
– Spasticity
Abnormal "models" of movements
– Presence of primitive reflexes
– Tonic labyrinthine reflex
– Symmetric and asymmetric tonic neck reflex
Inability for voluntary single movements
– Multiple involuntary movements in response to sensory stimuli
– Abnormal and inappropriate models of coordination
– Reduced ability for coordinate and dexterious movements

of spasticity and promote the manifestation of primitive reflexes and anorthodox movements; these interfere with and define the subsequent type of motion and gait. In rehabilitation programs for children, special care should be given for keeping the head in the right position, for avoiding scoliosis, and for allowing normal growing of the skeleton; the use of extended supporting orthoses ensures the continuation of skeletal development and prevents the development of abnormal postures [47]. Spastic paralysis of cerebral origin constitutes a typical paradigm; its clinical findings affect substantially the level of body functionality (Table 1). Usually, the correction of head position is sufficient for normalizing the muscle tone and reducing the elicitation of primitive reflexes. For example, the correction of spasmodic torticollis by injecting botulinum toxin in the ipsilateral sternocleidomastoid muscle and the use of cervical collar for supporting contralateral trapezoid muscle a week later may regulate body's increased muscle tone and reduce substantially abnormal movements. In children, the management of generalized and regional spasticity at early stages is of paramount importance since their cerebrum needs to record ''normal models'' of movement during the growing process [18]; importantly, this is beneficial for children's psychosomatic development as well [7].

Transition from the loose to the spastic phase

The presence of increased muscle tone in paralyzed limbs and trunk practically signals the maturation of the neural processes and the transition to the late stage of the underlying disease. In the early stage, spasticity influences positively the global neurological state of the patient, whereas, as the disease progresses, it aggravates the general functional performance (Table 2). The degree

Table 2. *Effects of spasticity on functional state*

Positive effects
– Preservation of balance and support to the trunk
– Elicitation of reflex movements
– Support of upright position and gait by extensor mechanism
– Maintenance of muscle mass
– Maintenance of mineral elements in the bones
– Reduction of lower limbs edema
– Reduction risks of deep vein thrombosis
Negative effects
– Deterioration of balance in upright position due to clonus, flexion spasm and spastic gait
– Deterioration of swinging phase of gait due to extension spasm and clonus
– Fatigue and weakness
– Slow voluntary movements of small range
– Sleep disturbances due to automatic movements
– Risk of fall from bed or wheel-chair
– Wrong posture in the bed or wheel-chair
– Bad hygiene of genitalia and difficulty in intercourse
– Difficulty in driving due to clonus and spasm
– Painful spasms

Table 3. *Factors that increase spasticity*

– Inflammation
– Reclining
– Urolithiasis
– Fractures
– Subluxations
– Ectopic ossifications
– Hyperactive cyst and vesiculoureter reflux
– Permanent catherization
– Syringomyelia
– Gradual progression of primary disease
– Menstruation
– Emotional instability
– Cold environment
– Particularly tight clothing

of spasticity may be influenced by both centripetal and nociceptive stimuli that affect the patient's symptoms (Table 3). Any sudden increase of spasticity necessitates the investigation for the potential presence of such stimuli; their effective management constitutes the first step in the course of a successful rehabilitation program [17]. The management of spasticity includes a wide spectrum

Table 4. *Aims of the management of spasticity*

– Relief from spasticity
– Improvement of functional capabilities
– Increase of mobility
– Relief from spasms-related pain
– Prevention of complications (e.g. cocontractures and pressure sores)
– Improved quality of life for patients and their carers
– Creater ease in nursing care

of measures from these that improve personal hygiene to treatments that modulate emerging pathophysiological processes. The main goals of an effective neurorehabilitation program are summarized in Table 4.

Oral medications

The pharmaceutical management of spasticity includes many drugs, which can alleviate muscle overactivity by reducing irritability of the motor fibers in the central nervous system (CNS), the neuromuscular junction or the muscle itself [49]. Initially, the antispastic drugs are administered orally in doses necessary for maintaining spasticity score lower than grade 1–2 in Ashworth scale [8]. The Food and Drug Administration (FDA) of USA has approved the following four substances for the treatment of spasticity: a) baclofen (in adults), which acts in receptors of the spinal cord, b) diazepame, which acts in the CNS, c) dantrolene, which acts in the neuromuscular junction, and d) tinazidine, which acts in the α2-adrenergic receptors located in the spinal cord and brain [25]. The oral administration of antispastic drugs is sufficient for cases of low-grade generalized spasticity; however, side effects associated with the level of arousal and liver metabolism do occur [25].

Physical and occupational approaches

The rehabilitation methods enhance the effects of drugs in reducing spasticity and also aim to preserve muscle elasticity. The preservation of the normal length and elasticity of the spastic muscle and the avoidance of the soft tissue shrinkage contribute to the prevention of subsequent contractures; to this effect, static and dynamic orthoses are used to develop the whole range of motion in the affected joint. The latter constitutes a fundamental element in achieving the functional re-education of affected limbs [40]. The reinforcement of antagonist over spastic muscles, which may be achieved by exercise or electrostimulation, reduces overactivity of spastic muscles and preserves their elasticity. It is important that the patient is aware of the applied techniques and actively participates in the management of spasticity and abnormal movements. Apart from intervention aiming to improve local synergy between muscle groups attached to adjacent joints, neurorehabilitation techniques play a key role in ensuring head and trunk balance and in facilitating postures that inhibit the production of abnormal reflective or massive movements [26]. Notably, when designing the therapeutic strategy and its goals, it is equally important to treat the negative sequelae of the upper motor neuron syndrome (UMNS) i.e. weakness, loss of coordination, and muscle fatigue. The usual physical and occupational approaches are: a) specific kinesiotherapy (facilitation techniques, proprioceptive methods, stretching, strengthening), b) physical modalities, c) electrical stimulation, d) electromyogram (EMG) bio-feed-back, and e) splints and casts.

Regional and focal management of muscle overactivity

Apart from the generalized spasticity, regional muscle overactivity also develops; this condition is a form of regional synergistic response or focal dystonia. The management of regional or focal spasticity is achieved by various means depending on the facilities and the available experience in modern modalities in each rehabilitation center. Decrease of regional spasticity may be facilitated by local injection of drugs causing chemical neurolysis. Such medications include: a) phenol, ethyl alcohol, and botulinum toxin type A (BTX-A) which produce neuromuscular block and b) lidocaine which results in perineural block [23]. In particular, lidocaine produces totally reversible effects of small duration and is used as a test before a selective neurotomy.

BTX-A is much more effective in reducing regional spasticity compared to other drugs that also cause chemical neurolysis. Its advantages are: 1) it may be used in outpatient clinics under local anaesthesia, 2) several muscle groups may be multiply injected in a single session, 3) the degree of spasticity is correlated to the injected drug dose, 4) the effects are reversible in case of overdose, and 5) neither sensory disturbances (in contrast to ethyl alcohol) nor permanent lesions develop [41].

In our department, chemical neurolysis by local injection of BTX-A is the first choice in the management of regional spasticity; it is a safe, effective, and well tolerated method, which may be incorporated in controlled therapeutic protocols. The benefits outbalance its high cost. The selection of muscles to be injected depends not only on the severity of spasticity but also, on the level of muscle participation in normal and immature motional patterns (synergies, synkinesias, co-existing movements, etc.) [39]. A consensus on the dosage has been recommended by the Spasticity Study Group [35]. A detailed description of the treatment by BTX-A is beyond the scope of this article [for a review see Refs. 16, 39, 42 and 44].

Intrathecal administration of baclofen by implanted pump

A considerable number of patients suffering from spasticity do not respond well to any available medical treatment or local chemical neurolysis. Administration of intrathecal baclofen (ITB) by implanted pump represents the most effective treatment for such severe cases [36]. ITB enhances the efficacy of the selected rehabilitation program by making feasible a new, more beneficial pattern of neurological adaptation and by promoting new mechanisms of neuroplasticity. The success of ITB is affected by several factors, which should be recognized and addressed before pump implantation. The most important pre-conditions are the close collaboration between physiatrists and neurosurgeons, the planning of rehabilitation program before and after pump implantation, and the existence of a supporting follow-up program. Pump implantation is considered successful when there is marked clinical and functional improvement, the patient is satisfied with his new life conditions, and the whole procedure is cost-beneficial [9].

Zahavi *et al.* have reported on the long-term effect (>5 years) of ITB on impairment, disability, and quality of life in patients with severe spasticity of spinal origin [50]; the most prominent improvements reported by the patients were increased ease of transfer, better seating posture, greater comfort in Activities of Daily Living (ADLs), decrease in pain, and increased efficacy of their neurorehabilitation programs [50]; it is estimated that ITB acts by reorganizing the brain networks or spinal cord tracts via mechanisms of neuroplasticity [1]. Given that ITB therapy may be beneficial for a wide range of disabilities, from ambulatory to vegetative states, it is mandatory that the treatment and functional goals must be individualized, clearly understood, and agreed upon with the patient, family, caregivers, and care-provider team before starting the treatment. Importantly, it is widely accepted that the patients who have been strictly selected and follow a clearly defined and realistic treatment program are likely to receive the biggest benefit from ITB therapy [19]. The management of spasticity in the conditions that most frequently cause this disability, namely spinal cord injury, multiple sclerosis, cerebrovascular disease and head injury is described in the following sections.

Multiple sclerosis

In multiple sclerosis (MS), lesions of the spinal cord are usually incomplete and the development of spasticity is influenced by the course of the disease [4]. Therefore, the management of spasticity should take into account the symptoms of the disease. Any chosen therapeutic approach should offer the possibility of altering the medical treatment according to the patient's symptoms and the goals of the neurorehabilitation program [28]. On clinical examination, a low degree of spasticity is commonly documented in supine position which is rapidly aggravated when standing, walking or doing body work. The treatment decisions should be preceded by meticulous clinical assessment and evaluation of the functional state of the patient in everyday activities. The combination of oral antispastic drugs with local BTX-A injections (adductor muscles, flexors of the foot and posterior femoral muscle) and the application of orthoses may improve substantially the patient's functional outcome [39]. Additionally, the management of spasticity greatly contributes to the decrease of fatigue and pain and the normalization of sleep. In MS cases, the major concerns are associated with the changing clinical patterns of the disease; the latter usually deteriorate, result to various clinical pictures and cause reduced functional performance and easy fatigue. Therefore, the management of spasticity should be individualized according to the patient's clinical state and the goals of the rehabilitation program at any given time.

Spinal cord injury

In patients with spinal cord injury (SCI), the phase of spinal shock ends when the first signs of UMNS become evident. The degree of spasticity depends on various factors clearly related to the type and severity of the lesion [15]. The management of spasticity is followed by a series of rehabilitation processes and practitioners should choose the appropriate treatment at any given time [31]. Occasionally, myelic automatisms are particularly pronounced as involuntary abrupt movements of the trunk and lower limbs; their intensity and frequency may be high enough to increase the risk of fall from the bed or wheelchair or to cause severe sleep disorders. In addition, the severity of spasticity in certain muscle groups (e.g. abductor) make personal hygiene, self-catherizations and everyday activities particularly difficult. From a neurorehabilitation point of view, profound spasticity of the lower limbs with co-existing painful movements facilitate the establishment of abnormal patterns of gait (in incomplete lesions) or hinder the placement of orthoses [39]. However, in incomplete SCI, the management of spasticity facilitates the education of motion and

the formulation of a more normal gait pattern through a long-lasting neurorehabilitation process [14]. A sudden increase of spasticity frequently implies another underlying disorder such as deep vein thrombosis, urolithiasis or infection. Notably, the general management of spasticity with implantation of a baclofen pump or local injection of BTX-A to the detrusor of the bladder may improve substantially the functional state of the sphincter of the cyst.

Cerebrovascular disease

The rehabilitation program in hemiplegic patients is a long-term process that consists of several stages [2]. Neuroplasticity research has shown that the management should rely on cognitive processes and repetitive treatments such as constrained-induced movement therapy to improve arm function [33] and treadmill training with partial bodyweight support and automated motor rehabilitation for gait education [26]. The success of any neurorehabilitation program is closely related to the effective management of general and local spasticity. In our department, the combination of mild oral regimes and local management of spasticity, in selected muscle groups, constitutes the treatment of choice. BTX-A is our prefered drug for inducing local chemical neurolysis and alleviating the symptoms of spasticity. Its injection under electromyographic (EMG) guidance achieves the long-term transition from an abnormal pattern of motion to coordinated functional movements and gait. This can be managed if only coexisting synergies, dyskinesias or synkinesias are reduced or eliminated. An effective therapeutic planning usually involves several sessions of drug injections in different muscle groups each time, the application of dynamic orthoses for gradual stretching of spastic muscles and a well-organized neurorehabilitation program.

The spasticity of selected muscles should be greater than grade 3 in the modified Ashworth scale [8]. However, in the case of biceps (the principal muscle in synergistic flexion of upper arm) or the posterior tibial (which is involved in the balance and pattern of gait), a spasticity grades 1–2 in Ashworth scale (when examined in reclining position and produce abnormal patterns of movement or gait) is sufficient indication for treatment by repeated injections of BTX-A. A week later, a dynamic orthosis of adjustable angle is applied in order to promote full stretching of the spastic muscle. A second series of BTX-A injections is offered 3–4 months later. The efforts to develop and ''educate'' mechanisms of gait, irrespective of the application of orthoses, greatly improves balance and body perception, while they activate neuroplasticity processes. The early management of local spasticity of key muscles following cerebrovascular disease, not only prevents complications and deformations of the joints, but also contributes to the functional balance between agonist and antagonist muscles; moreover, it modulates massive abnormal movement towards a ''normal'' pattern.

Disorders of muscle tone can be interrelated with disorders in proprioception and stereoagnosia. Special attention has recently been given to techniques improving the sensory function in parallel to the motional education. When atrophy develops in antagonist muscles due to disuse and constant overfunction of the agonist muscles, electrical stimulation followed by assisted exercises are the treatment of choice in order to increase muscle mass and strength. After a long period of muscle disuse, EMG bio-feedback is an effective method to study and improve the existing pattern of motion. In general, after the assessment of local and generalized spasticity, a neurorehabilitation program should involve learning processes that are based on repeat-attention-reward methodology and education over time [38]. The main goals of such a program are: a) the acceleration of ''automated'' recovery processes and b) the transformation of the ''immature'' pattern of motion and the guidance of the recovery process towards a state of neurological maturity. These will contribute to the development of a new ''physiological'' model; they will also ensure equilibrium between the patient's perceptions of environment body motion, and everyday activities and, hence, lead to a better adaptation to the new conditions of life [3].

Head injury

Severe head injuries can result to incomplete spastic tetraplegia with lateralization of symptoms and local muscle atrophy due to disuse or peripheral nerve damage. Body weakness and loss of muscle mass due to malnutrition further aggravate the general condition of the patient and may lead to severe sequelae such as ulcer decubitus and muscle contractures. The latter may also contribute to ectopic ossifications in hips, knees, and elbows. After severe head injuries, motor dysfunction may present with loss of coordination, decrease in movement range, increased spasticity and extrapyramidal signs. Moreover, patient's functionality is further reduced by cognitive disorders, difficulty in food uptake, existing tracheostoma, disorders of autonomous nervous system,

imbalance of head and trunk and many others. Coexisting untoward effects in terms of contractures, ectopic ossifications, and ulcer decubitus prolong the recovery period, necessitate specific nursing care and surgical interventions, and limit the efficacy of the neurorehabilitation program. Oral administration of antispastic drugs is usually insufficient in reducing generalized spasticity, while such drugs may affect negatively the patient's level of consciousness. Local injections of BTX-A greatly contribute to the increase of motion range in selected joints and the application of dynamic orthoses; however, this therapeutic approach does not apply in cases of generalized spasticity, since multiple injections will also increase drug serum concentration above therapeutic levels [20].

In our Unit, the preferred therapeutic approach includes oral administration of baclofen and local chemical neurolysis, depending on the phase of the rehabilitation program. The following therapeutic goals are highly regarded: a) the combination of biphosphate and indomethacin for reducing ectopic ossification in early stages, b) the analgesic drugs, c) the food intake balance, d) the treatment of coexisting osteoporosis or fractures, e) the alleviation of ulcer decubitus, and f) the prevention of infections. In particular, these parameters greatly contribute to the preservation of body posture in bed or wheelchair. Furthermore, re-education of speech, communication and shallowing, as well as participation of the patient in everyday activities in sessions of speech therapy and ergotherapy also constitute key elements of an effective neurorehabilitation program. In many cases of generalized spasticity following severe head injury, the implantation of a baclofen pump represents the treatment of choice. ITB administration permits continuous regulation of spasticity in all affected muscle groups, particularly in cases of spastic tetraplegia [5]. The overall management of spasticity increases dramatically the efficacy of any neurorehabilitation program in terms of reducing complications and augmenting motional, cognitive, and functional performance of the sufferer. The right position of the patient on the wheel-chair is of paramount importance for improving the functional outcome. In particular, it facilitates head and trunk balance, improves coordination of upper limbs, augments proprioceptive inputs, allows education of fine movements, and ensures patient's re-entry in everyday activities. Moreover, speech therapy, education of cognitive functions, swallowing and breathing is positively influenced. Ideally, pump implantation should be scheduled when the 'phenomenon' of spasticity has fully developed and soft tissue transformations have not become too severe or irreversible [19, 21].

When the degree of spasticity is low, a series of corrective orthopaedic procedures may be offered in order to improve the patient's functional outcome. These may include arthrodesis of a deformed joint in a functional position, functional tenontometatheses (e.g. flexors to extensors of lower limb), resections of ectopic ossifications in a locked joint, correction of scoliosis etc. These procedures are greatly facilitated if the daily dose of ITB is increased [29, 30]. The daily baclofen dose should be adjusted to the particular goals of the neurorehabilitation program and the degree of spasticity; both of them are closely related to the disease progression and the patient's functional state [45]. In cases of head injury, in particular, it is commonly needed to adjust daily baclofen dose several times before the date of the regular refill. Apparently, from a practical and medical point of view, programmable pumps have a remarkable advantage over other pump types; given that their adjustment does not require their refill, the risk of infection is considerably lower.

Our experience in spastic tetraplegia after head injury

During the period 2000–2005, 104 patients were admitted to our unit because of severe head injury. Eight of 104 patients developed incomplete spastic tetraplegia and were considered as suitable candidates for a baclofen programmable pump implantation (Synchromed, Medtronic, Minneapolis, USA). Five patients were males and three females and their age ranged from 14–64 years (mean age $= 29.5$ years). The interval between the event of neural impairment and the pump implantation ranged from 105 days to 9 years (mean time $= 2.53$ years). The post-implantation follow-up period varied from 3 to 63 months (mean follow-up period $= 1{,}73$ years). The mean daily dose required for the relief of spasticity was 194 μg, and the mean number of pump refills was six. All eight patients experienced considerable decrease in spasticity (by 1–2 grades in Asworth scale) and significant improvement in cognitive function, speech, oral feeding, and body posture. Importantly, in two patients suffering from contracture in the ankle joint, the pump implantation permitted a corrective arthrodesis with tenontometathesis to be performed at a later stage. With respect to functional performance, all 8 patients could stand in upright position when supported appropriately, while 4 of them were able to walk

between horizontal bars. Following pump implantation, all patients could sit on a wheelchair, found easier their personal hygiene, experienced less pain and discomfort, were able to sleep for longer periods and their families described that they could help the patients in a more effective and easier manner. Although this is small patient cohort, the consistency of the results does indicate the great significance of a management approach that combines both neuromodulation and neurorehabilitation approaches.

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Epidural spinal cord stimulation in lower limb ischemia

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Summary

Epidural spinal cord stimulation (SCS) has been used as a method to improve microcirculatory blood fow, relieve ischemic pain and reduce amputation rate in patients with severe peripheral arterial occlusive disease (PAOD). In this article, the theories attempting to explain the mechanisms of SCS vasoactive action are presented. Our method of patient screening and our surgical technique for SCS implantation are described. In addition, the various published series reporting on the efficacy of SCS in PAOD are critically reviewed. The contemporary reports demonstrate the efficacy of SCS in ischemic pain relief. In the light of these results and our own experience, we conclude with an appraisal of modern techniques for assessing critical limb ischemia.

Keywords: Neuromodulation; spinal cord stimulation; SCS; epidural stimulation; lower limb ischemia.

Introduction

Epidural Electrical Spinal Cord Stimulation (SCS) has been used as a method to improve microcirculatory blood flow, relieve ischemic pain and reduce amputation rate in patients with severe peripheral arterial occlusive disease (PAOD). Vascular reconstruction is the treatment of choice for patients with severe PAOD classified as Fontaine's stages IIb (claudication free interval less than 50 m), III (chronic ischemic rest pain) and IV (ischemic pain ulcers and/or dry gangrene) [17, 44]. Advances in interventional arteriography and vascular surgery have resulted in increased limb salvage rates. Despite this undeniable progress, the number of patients with non reconstructible lesions remains high [20] with 60.000 major amputations performed yearly in the United States. It is estimated that 10–30 per cent of patients with chronic critical limb ischemia will die within 6 months of its onset and another 25–35 per cent will undergo a major amputation [11]. Ideal treatment in these stages allows the patient to retain his limb with no pain or tolerable pain and to regain a satisfactory level of independence. SCS was used initially into clinical practice to manage patients with chronic intractable pain or to improve motor function in patients with partial spinal cord lesions [9, 38, 50]; in the United States over 100.000 pain patients have received SCS treatment with varing success. Several authors observed a marked improvement in lower limb blood flow in a group of patients who were being treated with SCS for pain related to multiple sclerosis. Based on these observations, SCS has attracted greater interest in the treatment of ischemic rest pain [2, 7] and in Europe common indications for SCS are refractory angina and peripheral vascular disease. Other authors have reported significant pain relief and healing of ischemic ulcers in patients with end-stage vascular disease who are receiving SCS [2, 3, 5, 6, 10, 13, 18, 21, 24]. In 1988, Jacobs *et al.* [27, 28] found that the number of capillaries perfused and the red blood cell velocity were significantly increased by SCS. Several noninvasive (Doppler, rheography, plethysmography, thermography, transcutaneous oxygen tension) and scarcely invasive (^{201}Tl muscle scintigraphy, xenon^{133} clearance) techniques have been applied in an effort to quantify the SCS effect on blood flow [16, 23, 29, 35, 47].

SCS in PAOD: mechanisms of action

There are several theories attempting to explain the mechanisms of action of SCS. The most common include: a) The "Gate Theory" of Melzak and Wall [38] with segmental, antidromic stimulation and activation of afferent a-Beta fibers, ii) the activation of the inhibitory center on efferent sympathetic neurons, c) the inhibition of transmission of the spinothalamic and supraspinal tract, and d) the release of neurotransmitters and neuromodulators through spinal cord stimulation. In 1973,

Cook and Weinstein [8] used SCS to treat pain in the lower limbs in patients with multiple sclerosis and found an increased distal blood flow in the limbs; after this, they started to use this technique in patients with PAOD. They found not only an improvement in pain, but also increases in arterial blood flow and temperature, and improved tissue survival and integrity. These studies were supported by the findings of Dooley and Kasprak [10] who demonstrated distal vasodilatation after dorsal medullary stimulation of the spinal cord. They therefore concluded that vasodilatation occurred by antidromic activation of e-fibers. Linderoth *et al.* [33, 34] also studied the potential mechanisms of action of the SCS and concluded that antidromic activation of C fibers was one of the possible mechanisms, but it did not appear to be the main one, because when the dorsal ganglia were sectioned in experimental studies, vasodilatation was still seen after SCS. This group postulated that the main mechanism of action of SCS is through the autonomic nervous system, specifically through inhibition of the part of the sympathetic system responsible for vasoconstriction. Vasodilatation will therefore be maintained by inhibition of the sympathetic nicotinic transmission at both the ganglionic and postganglionic level. This theory is important and supported by evidence in animal studies following nerve section, alpha adrenergic blockade or bilateral lumbar sympathectomy, and in humans suffering from diabetic autonomic neuropathy. In the presence of the described sympathectomy, all demonstrated maximum vasodilation, therefore the SCS could not achieve the vasodilating effect through the same mechanism as in subjects with an intact sympathetic system. Other potential mechanisms have been proposed and include the release of vasodilatory mediators such as vasoactive intestinal peptide (VIP), substance P, calcitonin, prostaglandins, and endothelium-derived factor [14, 25]. However, none of these mediators have been shown conclusively to be the primary mediator of SCS-induced vasodilation.

Implantation technique

A multipolar electrode is placed in the epidural space by percutaneous lumbar puncture between L2 and L3 or L3 and L4. The electrode is advanced under fluoroscopic guidance up to the level T10–11. The midline placement is preferred in most cases. Connecting a portable stimulator to the electrode allows intraoperative test stimulation producing comfortable paresthesias in the painful foot or limb. The clinical effects are tested during a trial period of 1 to 4 weeks. If the patient has a significant pain relief, an implantable pulse generator is placed in an abdominal subcutaneous pocket. Various settings of the active quadripolar ends of the electrode are studied to evaluate the most appropriated combination for the patient's pain relief. Bipolar stimulation is assessed by the presence of paresthesias and a feeling of warmth in the painful area. The setting parameters are as follows: a) pulse amplitude between 1.0 and 5.0 V, b) frequency between 40 and 120 pps, and c) pulse width from 150 to 450 msec. Stimulation is continuous, 24 hours a day, to obtain maximum information on the clinical result. During follow-up, the parameters of stimulation can be reset with the help of a portable computer, according to the patient's clinical state.

Efficacy of SCS in published series

We report on 16 SCS studies, involving 683 PAOD patients, that included prospective randomized controlled or prospective controlled studies ($n = 2$) (Table 1a), prospective studies with no controls ($n = 4$), and retrospective studies ($n = 10$) (Table 1b). Klomp *et al.* (1999) [31] examined 120 patients randomly assigned to either SCS with best medical treatment or best medical treatment alone. All patients were diagnosed with critical limb ischemia. The purpose of the studies was to examine the role of SCS in the treatment of ischemic pain and the prevention of amputation. The mean follow-up was 19 months. Results did not show any significant improvement in pain scores between the two groups. However,

Table 1a. *Prospective randomized controlled or prospective controlled studies*

Author	Indication	Patients	Mean follow-up	Group [patients number]	Narcotic use	Success
Jivegard (1995)	ischemic limb pain	51	18 (ms)	SCS plus peroral analgesic treatment [25]; peroral analgesic treatment only [26]	not collected	pain scores of SCS vs. control ($p = 0.01$)
Klomp (1999)	ischemic limb pain	120	19 (ms)	SCS plus best medical treatment [60]; best medical treatment only [60]	pain medication reduced in SCS group $p < 0.005$	both groups significantly reduced their pain score compared to baseline ($p < 0.001$)

Table 1b. *Retrospective or prospective studies with no matched controls*

Author	Indication	Patients	Follow-up (ms)	Success
Prospective studies with no matched controls				
Graber (1987)	ischemic limb pain	9	7	80%
Horsch (1994)	ischemic limb pain	177	35.6	78%
Petrakis (2000)	ischemic limb pain	60	18	78%
Rickman (1994)	ischemic limb pain	25	6	72%
Retrospective studies				
Kumar (1998)	ischemic limb pain	29	66	69%
Meglio (1989)	ischemic limb pain	19	12	100%
Spiegelmann (1991)	ischemic limb pain	2	13	100%
Bracale (1989)	ischemic limb pain	27	unknown	80%
Broseta (1986)	ischemic limb pain	37	25	81%
Fiume (1989)	ischemic limb pain	45	48	64%
Francaviglia (1994)	ischemic limb pain	15	12–72	78%
Huber (1996)	ischemic limb pain	17	32	100%
Petrakis (1999)	ischemic limb pain	150	71	75%
Sampere (1989)	ischemic limb pain	17	2–27	71%

Table 2. *Complications of SCS in PAOD*

Complication	Number of events	Total number of patients	Rate of occurrence (%)
Lead migration	111	789	14.0
Infection	32	834	3.8
Epidural hemorrhage	0	834	0.0
Seroma	0	834	0.0
Hematoma	4	834	0.5
Paralysis	1	834	0.1
CSF leak	48	834	5.8
Undesirable stimulation	13	789	1.6
Intermittent stimulation	0	789	0.0
Pain over implant	2	789	0.3
Allergie reaction	2	789	0.3
Skin erosion	3	789	0.4
Lead breakage	24	789	3.0
Hardware malfunction	15	789	1.9
Loose connection	0	789	0.0
Battery failure	11	789	1.4
Other	16	755	2.1

the amount of pain medication was significantly reduced in the SCS groups ($p < 0.05$). Jivegard *et al.* (1995) [30] also examined the effects of SCS on a group of 51 patients with chronic limb ischemia. Patients were randomized either to a group that was treated with oral medication and SCS or to one that was treated with oral medication only. This study reported a significant improvement in pain scores of the SCS group compared to the non-SCS group ($p = 0.01$). Four studies were prospective without matched controls [19, 24, 42, 44]. The follow-up ranged from 6 to 35 months for a total of 271 patients. One study examined the effectiveness of SCS on 177 patients over a period of 35 months [24]. Success was defined as either greater that 50% pain relief using a 4 or 5 point scale, or a significant reduction in VAS scores. They success rate was 78% in this population. The average success rate for all studies in this group was 78% (210/271). Ten studies were retrospective without matched controls [4, 6, 12, 15, 26, 32, 38, 41, 46, 50]. The mean follow-up ranged from 2 to 72 months. An analysis of all twelve studies gave a success rate of 67% (274/412). All the complications reported in these studies are shown in Table 2. No serious adverse events were identified in any of the series. The most common complication was lead migration (14%). The introduction of multichannel leads has greatly reduced the need for reoperation because of lead migration. North *et al.* [40] found that programmable multichannel systems have significantly greater clinical reliability than single-channel systems. Alo and Holsheimer[1] reported that of their patients who stopped having paresthesias, only 3.8% required revision of lead placement to improve the clinical efficacy. They claimed that this was the result of using the eight-electrode lead and complex programming. The remaining complications were found to occur in less than 6% of the time, with nine complications occurring in less than 1% of the time or not at all.

Discussion

The contemporary reports demonstrate the efficacy of SCS in ischemic pain relief. Recently a systematic review and meta-analysis of controlled trials assessing SCS for inoperable critical leg ischemia demonstrated that the addition of SCS to standard conservative treatment improves limb salvage, ischemic pain and the general clinical condition in patients with inoperable chronic critical leg ischemia [52]. In our opinion, SCS should not be used to treat patients affected by extensive gangrenous lesions of the foot (classified in Fontaine's IVb stage). In these patients, who are neither responders to medical treatment nor amenable to vascular reconstructions, the recommended treatment, in agreement with other authors [53], is primary amputation. In the presence of severe nociceptive somatic pain, the analgesia induced by SCS is less effective than this achieved with epidural anaesthetics with or without opiates. With respect to patients affected by claudication only, SCS is indicated if their pain-free walking interval is less than 50 meters (Fontaine's IIb stage patients) and if the other therapeutic options have

definitely been exhausted. The presence of diabetes does not represent a contraindication to the use of SCS.

The exact mechanism that underlies the effect of SCS on chronic and ischemic pain remains unclear. The gate control theory proposed by Melzack and Wall [38], in 1965, has been used widely to explain the action of SCS. This theory postulated that an inhibitory mechanism in the dorsal horn is activated by the recruitment of large-diameter fibers. The substantia gelatinosa activation induces inhibition of second-order neurons processing nociceptive information. Presently, the mechanisms proposed to be responsible for pain relief are neurophysiological and neurochemical in nature. The neurophysiology of pain relief by SCS varies from: a) simple blocking of pain transmission by a direct effect on spinothalamic tracts, b) segmental inhibition via coarse fiber activation, c) effects on central sympathetic systems, and d) brain stem loops to thalamocortical mechanisms [22]. The inhibitory effects of SCS on the transmission of nociceptive impulses may be exerted segmentally in the spinal cord and/or at a supraspinal level [33, 34]. Clinical observations indicate that the mechanisms involved in the stimulation-induced relief from ischemic pain are different from those related to relief from others types of pain [39]. Indeed, nociceptive pain is more resistant to SCS, and significant pain relief is almost never obtained before a couple of days. In contrast, neuropathic pain of peripheral origin responds well and immediately to SCS. Both components, nociceptive as well as neuropathic are present in ischemic pain. Several authors have postulated that the principal factor in the relief of ischemic pain is the inhibition of the pain signal per se, leading to both a decrease in sympathetic activity as well as improved skin microcirculation [6, 25, 39].

During the testing period, in addition to pain control, the effect on peripheral blood flow must be carefully assessed to ascertain if the warmth feeling, reported by the patient, is related to increased skin microcirculation. This assessment should include determination of the pain-free walking interval under standard conditions (treadmill), confirmation of ulcer healing (surface measurements) and verification of improved blood flow. The most useful instrumental techniques for peripheral vascular screening during SCS are plethysmography and transcutaneous PO_2 ($TcPO_2$) [6, 27, 28, 48, 51]. The decrease of ischemic pain with SCS is probably secondary to the positive effects on microcirculation rather than vice versa. Pain relief may also result mainly from the attenuation of sympathetic activity with vasodilatation, leading to additional pain relief [34]. In critical limb ischemia, the aim of SCS is not only to achieve effective analgesia (which might be obtained by other less expensive techniques), but also to promote the trophic-functional recovery of the body segment affected by an advanced ischemic process. Another hypothesis is that SCS suppresses autonomic sympathetic activity [34, 36]. However, many authors have reported success even after sympathectomy [86, 7, 25, 30] and SCS has been shown to be useful in vasospastic disease and reflex sympathetic dystrophy [45]. $TcPO_2$ is a non invasive method suitable for accessing skin circulation and was chosen to evaluate microcirculatory changes induced by SCS [35, 48]. In patients with salvaged limbs, $TcPO_2$ values showed an overall increase following stimulation. After SCS, $TcPO_2$ on the dorsum of the foot increased significantly, whereas the ABI did not change under stimulation. The feeling of warmth in the painful area under SCS was related to an increase in $TcPO_2$. $TcPO_2$ measurements allow evaluation of the effects of SCS on microcirculatory blood flow and represent a strong predictor of success as an increase in $TcPO_2$ >50% in the first 4 months correlates well with a positive clinical result [47].

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Spinal cord stimulation in the treatment of chronic critical limb ischemia

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Summary

This paper reviews the clinical experience and proposed working mechanisms of spinal cord stimulation (SCS) in the treatment of chronic critical limb ischemia (CCLI). SCS appears to provide a significant long-term relief of ischemic pain and to improve healing of small ulcers, most likely due to effects on the nutritional skin blood flow. Despite these observations, randomized trials were not able to show limb salvage. Assessment of the microcirculatory skin blood flow, by means of transcutaneous oxygen pressure measurements and videocapillaromicroscopy, is necessary to evaluate the remaining microcirculatory reserve capacity likely to be exploited by SCS and to help identify patients that will benefit most from this treatment and in whom stimulation could lead to limb salvage.

Keywords: Spinal cord stimulation; ischemic pain; pain relief; chronic critical limb ischemia.

Introduction

Percutaneous angioplasty and/or bypass procedures are treatment options of choice in patients with CCLI. [46] Despite the abundance of therapeutic procedures, there are still patients in whom conventional strategies of management have been exhausted.

The rationale for the use of SCS in the treatment of chronic pain originates from the ''Gate Control Theory of Pain'' proposed by Melzack and Wall in 1965 [45]. In 1967, Shealy introduced SCS into clinical medicine to treat chronic neurogenic pain syndromes [48]. The feasibility of chronic neural stimulation greatly increased when the technology developed for cardiac pacemakers was transferred to implantable neural stimulators. SCS has been used for pain due to peripheral vascular disease for 25 years. The pioneer articles by Cook *et al.* and Dooley *et al.* in 1976 reported effective relief of ischemic pain and healing of ischemic ulcers by SCS [15, 18]. Since then, clinical application of electrical neurostimulation has widened to spinal cord, intrathecal or peripheral nerve stimulation as well as other indications like vasospastic disorders, sympathetic reflex dystrophy, angina pectoris, epilepsy, Parkinson's disease and urinary incontinence.

Over the following decades, several non-controlled studies reported significant pain relief, improved ulcer healing and skin blood flow in patients with peripheral vascular disease [2–5, 20, 22, 24, 26, 30, 44, 50]. Due to lack of a control group, the efficacy of SCS could not be proven and randomized controlled studies were needed.

A spinal cord stimulator consists of an electrode lead, an extension lead and an implantable pulse generator (IPG). Low-voltage electrical pulses, generated by the IPG, are conducted to the multipolar lead placed in the epidural space. Implantation of the multipolar electrode lead is performed under local anesthesia by percutaneous lumbar puncture. The lead is advanced in the epidural space under radioscopic control to the level of Th 11–12. Midline placement of the lead is preferable. During intraoperative stimulation, the patient often reports a pleasant and warm sensation in the painful area. During a trial period the clinical effects are monitored and if adequate pain relief is observed, the IPG is placed in a subcutaneous pouch in the iliac fossa. The generator is programmed by an external computer, and the usual pulse settings are amplitude between 0.5–2.0 V, frequency between 70–120 Hz, and pulse width of 210 μs. Stimulation can be given continuously or intermittently. The patient is able to activate and deactivate the IPG and to adjust the pulse amplitude with the use of an external programmer. During follow-up the parameters can be reset with the help of the portable computer. This review

presents the possible mechanisms of action, discusses the selection of patients and gives an overview of the clinical effectiveness of SCS in the treatment of CCLI.

Physiological mechanisms modulated by SCS

The effects of SCS on pain are based on the ''Gate Control Theory of Pain'' proposed by Melzack and Wall in 1965 [45]. This theory describes a model in which the nociceptive, small diameter afferents are inhibited by stimulation of non-nociceptive myelinated Aβ-fiber afferents. Wall *et al.* and Shealy *et al.* were the first to postulate that electrical stimulation of the nervous system could serve as a tool in the treatment of pain [48, 53]. Although the concept of this theory is no longer tenable in all its aspects, the idea of suppressing noxious evoked activity by modulating myelinated non-nociceptive afferent Aβ-fibers remains unchanged.

The inhibitory effects of SCS on the transmission of nociceptive impulses may be exerted segmentally in the spinal cord, at a supraspinal level – or both. It is likely that several mechanisms are active simultaneously. At present, several hypotheses are discussed. [14, 38] The hypothesis that the relief of ischemic pain is due to direct inhibitory effects of electric stimuli applied to the dorsal columns on the transmission of nociceptive impulses from the dorsal horn to the brain via the spinothalamic tracts, is supported by the results of different neurophysiological experiments. [21, 27] However, these results have to be interpreted with caution because these experiments use ''acute peripheral nociceptive conditions'' and on the other hand it is difficult to adapt stimulation parameters to those used in clinical practice. Another hypothesis implies that vasodilation during stimulation depends on the same mechanisms that account for the vascular response recorded when the dorsal roots or peripheral nerves are antidromically stimulated with very high intensity. Several groups proposed that the effects were due to the release of substances from thin nerve fibers, like prostacyclin, substance P, and calcitonin gene-related peptide (CGRP) [25, 38]. This hypothesis of antidromic stimulation is controversial. Indeed, experimental studies indicate that neither antidromic activation of primary afferents nor recruitory are responsible for the stimulation-induced vasodilation. [36, 37] However, it was also shown that SCS-induced vasodilation can occur through mechanisms independent of efferent sympathetic nervous system activity and that antidromic vasidilation may be recruited with a slightly higher stimulation intensity, probably mediated via Aδ-fibers [16, 17]. Several other studies have provided evidence for the involvement of neurotransmitters in the pain relieving effects of SCS [32, 33, 40]. Substances of special interest are vasoactive intestinal polypeptide (VIP), serotonin, substance P, noradrenaline, calcitonin gene-related peptide (CGRP), gamma-amino-butyric acid (GABA), prostaglandins and nitric oxide (NO) [38, 39, 41]. GABA is considered a major inhibitory spinal transmitter involved in pre- as well as postsynaptic inhibition at the terminals of primary afferents, both of large diameter and of thin unmyelinated fibers subserving nociception. Substance P and CGRP are probably primary transmitters in the dorsal horn of the spinal cord, but they can also be released in the periphery by antidromic stimulation. Both substances are vasodilators and increase vascular permeability. The observed pain relief in ischemic conditions may also be the result of the modulatory action of SCS on the activity of the autonomic nervous system, more specifically by inhibiting the sympathetically maintained peripheral vasoconstriction mediated via nicotinic ganglionic receptors and α 1-adrenergic receptors [37]. Another hypothesis postulates the activation by SCS of supraspinal pain modulatory centers involved in antinociception. Descending inhibition of neurons in the spinal dorsal horn can be elicited from the mid-brain, e.g. the periaqueductal gray and the nucleus raphe magnus. The descending inhibitory systems can be activated by electrical stimulation of the spinal cord [54].

Patient selection

Clinical classification of the vascular patient considered for SCS is based upon the criteria published in the European Consensus Document [19] on Chronic Critical Leg Ischemia and the TransAtlantic Inter-Society Consensus (TASC) [43] Document on the Management of Peripheral Arterial Disease. CCLI is defined by the fol-

Table 1. *Clinical classification according to the European consensus document/TASC document*

Persistently recurring ischemic rest pain requiring analgesia for more than 2 weeks and/or ischemic ulceration or gangrene (less than 3 cm^2)
– Ankle systolic pressure <50 mmHg
– Ankle/brachial index <0.4
– Toe systolic pressure <30 mmHg
– Diabetics: absence of distal pulsations
Further evidence of ischemia by:
– Intra-arterial angiogram
– $TcPO_2$ <30 mmHg

Table 2. *Patient selection for SCS in CCLI*

– Clinical classification
– Screening of the microcirculation
– Non-reconstructable CCLI
– Patient cooperation
– Life expectancy greater than 6 months
– Significant pain relief as demonstrated by trial screening
– Informed consent

SCS Spinal cord stimulation, *CCLI* chronic critical limb ischemia.

lowing two criteria: persistently recurring rest pain requiring regular analgesia for more than two weeks and/or ulceration or gangrene of the foot or toes, with ankle systolic pressures less than 50 mmHg (Table 1). The main subjects to be selected for SCS are patients with severe ischemic pain at rest. Patients who have significant tissue loss respond less successfully to SCS. Nociceptive ischemic pain due to small ulcers or gangrene ($<3\,cm^2$) may respond to SCS. The macro- and microcirculatory parameters should be consistent with CCLI: ankle brachial index (ABI) <50 mmHg, toe systolic pressure <30 mmHg and $TcPO_2$ <30 mmHg (Table 2).

In all patients, a complete vascular work-up is mandatory in order to provide baseline information. A full vascular history is taken as well as a complete physical exam and careful assessment of the patient's pain. Methods that can be used for pain measurement are e.g. the visual analogue scale, the verbal rating scale and procedures to specify the qualities of pain like the McGill Pain Questionnaire. Vascular tests included segmental Doppler arterial waveforms, ABI, ankle systolic pressure, toe systolic pressure, $TcPO_2$, laser Doppler fluxmetry, and videocapillaromicroscopy.

Patients with rapidly progressing ischemia, extensive gangrene/ischemic ulcerations with underlying osteomyelitis or local infection, poor compliance, or presence of concomitant disease reducing life expectancy are excluded. SCS is definitely not an alternative to bypass surgery and an ischemic limb can be considered technically non-reconstructable only if the angiogram, in addition to the missing arteries, demonstrates a collateral circulation down to the level of the foot.

In order to benefit from the therapy, the patient must be able to understand the concepts of the therapy and he must be willing to accept the paresthesia under stimulation. But they must also be able to handle the system (to switch ''on'' and ''off'' with a magnet) or to adjust the parameters of stimulation with a magnet. Considerable time and effort is required to educate and train the patient and his family.

Clinical results

Non-randomized trials

The first report of a larger series was made by Augustinsson *et al.* who in 34 patients with ischemic pain reported excellent or good pain relief (>75% pain relief) in 90% of cases [2]. Other studies have reported similar results with good pain relief in 80% of patients (Table 3). Not only patients with vascular disease due to atherosclerosis were treated, but also patients with vasospastic vascular disease (Raynaud's disease) or thrombangiitis obliterans (Buerger's disease). Healing of arterial ulcers was reported, suggesting an improvement of the nutritional skin blood flow. It was shown that after SCS, the number of skin capillaries perfused had increased as well as the skin capillary red blood cell velocity [28, 29]. Other studies evaluated effects of SCS on $TcPO_2$ showing that $TcPO_2$ changes correlated with the presence of adequate paresthesia in the painful area [6, 9, 11, 13, 23, 26, 35, 47]. However, it is difficult to generalize the data obtained from uncontrolled studies so randomized controlled trials were needed [42].

Table 3. *Pain relieving effects of SCS in published series*

Author (year)	No. of patients	Follow-up	Pain relief (%)
Augustinsson *et al.* (1985)	34	mean 16 mo.	>90
Groth (review) (1985)	117	mean 13 mo.	>90
Broseta *et al.* (1986)	41	up to 25 mo.	70
Broggi *et al.* (1987)	46	–	±70
Jivegård *et al.* (1987)	32	mean 27 mo.	90
Galley *et al.* (1988)	23	up to 27 mo.	±60
Jacobs *et al.* (1990)	20	up to 36 mo.	60
Meglio *et al.* (1989)	40	mean 19 mo.	90
Horsch and Claeys (1994)	177	mean 36 mo.	62
Claeys (1997)	237	mean 31 mo.	73
Kumar *et al.* (1997)	39	up to 36 mo.	77

SCS Spinal cord stimulation.

Table 4. *Randomized studies on SCS in CCLI*

Author (year)	Diabetics (%)	Limb salvage SCS (%)	Limb salvage control (%)	Patients	Follow-up
Suy *et al.* (1994)	21	68	40*	38	20 mo.
Jivegård *et al.* (1995)	10	62	45*	51	18 mo.
Claeys and Horsch (1996)	13	85	80*	86	12 mo.
Klomp *et al.* (1999)	37	50	42*	120	24 mo.

* Not significant.
SCS Spinal cord stimulation, *CCLI* chronic critical limb ischemia.

Randomized trials (Table 4)

The "*Belgian multi-center study*" included 38 patients with severe CCLI unsuitable for vascular reconstruction [49]. Patients were randomized as follows: 20 for SCS and 18 for further conservative treatment. All patients received "optimal medical treatment" consisting of anti-aggregation therapy and analgesic medication. Mean follow-up was 20 ± 15 months. Life table analysis did not show a significant difference in forefoot salvage up to 24 months (only about 5%), although there was a trend towards a difference thereafter. When evaluating "clinical success" (quality of life, significant pain relief, ability to walk, foot salvage), the SCS-group did significantly better ($p < 0.05$). SCS-patients seemed also to be protected by SCS as no late amputations were noted. Patients who continued to smoke had a bad prognosis, independent of the type of treatment.

The "*Swedisch multi-center study*" included 51 non-reconstructable patients with CCLI (including 10 diabetics) randomized to either "SCS + peroral analgesic medication" ($n = 25$) or "peroral analgesic treatment alone" ($n = 26$) [31]. During the study period approximately 1000 patients underwent bypass surgery at the two involved vascular centers. Endpoints were limb salvage (no or minor amputation), amputation rate within 18 months, and pain relief. Macrocirculatory parameters were not different in the two groups during a follow-up period of up to 18 months. Microcirculatory parameters were not investigated. Long-term pain relief was observed only in the SCS-group. At 18 months, a 17% difference in foot salvage was observed, 62% with SCS, and 45% without SCS. This difference was not statistically significant because of the small sample size. Subgroup analysis suggested a better limb salvage in normotensive patients.

The "*Cologne single-center study*" included 86 non-reconstructable patients (including 13 diabetics) with CCLI who were treated with seven days intravenous prostaglandin E1 (PGE1) and were subsequently randomized into receiving two weeks PGE1 with or without SCS. [7, 8, 10, 12]. Entry criteria included: severe CCLI with ankle systolic pressure <50 mmHg, foot $TcPO_2$ <20 mmHg and unrelenting rest pain despite analgesic medication, proof that surgery or angioplasty were impossible by angiogram or patient condition, and the presence of nonhealing foot ulcers or dry gangrene. At 12 months there was significantly better total healing of foot ulcers in the SCS-group: 69 vs. 17% ($p < 0.0001$), and more SCS-patients achieved an outcome of Fontaine stage II, 40 vs. 10% ($p = 0.0014$). However, the frequency of minor and major amputations was not different, respectively 13 vs. 15% and 16 vs. 20%. The mean ankle/brachial index at 12 months of the treated limb of the SCS-patients was not significantly greater. The healing was most likely due to increase in microcirculatory blood flow as foot $TcPO_2$ rose 213% in the SCS group and fell 2% in the control group ($p < 0.0001$). A $TcPO_2$ increase above 26 mmHg correlated with ulcer healing, whereas a $TcPO_2$ less than or equal to 10 mmHg predicted poor outcome.

The "*Dutch multi-center study*" enrolled 120 patients with non-reconstructable CCLI during 3 years [34, 51, 52]. Treatment strategies were "optimal medical treatment" versus "SCS + optimal medical treatment". Primary endpoints were limb salvage, pain relief, quality of life and cost-effectiveness. Secondary endpoints were healing of ischemic lesions, level of amputation, effects on the macro- and microcirculation and complications. A 2-year follow-up revealed no statistically significant differences with regard to limb salvage, pain reduction or improvement of quality of life. It was concluded that with selection methods based on clinical and macrocirculatory parameters, no superiority of SCS could be proven over a good organized conservative approach. However, microcirculatory parameters seemed to be a predictor of limb salvage under SCS. Limb survival at 12 months was 17% in the "*poor*" group, 63% in the "*intermediate*" and 88% in the "*good*" group, indicating a high predictive value of microcirculatory classification as to an imminent amputation. ("*poor microcirculation*": capillary density: <20 perfused capillaries/mm^2; absent reactive hyperaemia in capillaromicroscopy and LDF, and $TcPO_2$ <10 mmHg; "*good microcirculation*": capillary density: >20/mm^2, present reactive hyperaemia and $TcPO_2$ >30 mmHg).

The "*European Peripheral Vascular Disease Outcome Study (SCS-EPOS)*" studied the effects of SCS on limb survival in patients with non-reconstructable CCLI [1]. Patient selection was based upon $TcpO_2$ and patients were divided into three groups. The SCS-Match group comprised patients with a baseline forefoot $TcpO_2$ of >30 mmHg and both sufficient pain relief and sufficient paraesthesia coverage after the test stimulation period. If baseline $TcpO_2$ was <10 mmHg, $TcpO_2$ should have exceeded 20 mmHg after test stimulation. The SCS-Match group was compared with patients not meeting these criteria, who were treated either with SCS or without SCS. In the SCS-Match group a significant improvement in pain relief and $TcpO_2$ was seen. After 12 months, cumulative limb survival of patients treated with SCS

was significantly better than that of patients not treated with SCS. Limb survival in the SCS-Match group was significantly higher than that in both other groups. It was concluded that patient selection, based on $TcpO_2$ and the results of trial screening, increases the probability of limb salvage after SCS therapy.

Discussion

Angioplasty and/or bypass grafting are the treatment of choice for limb salvage in patients with CCLI, and limb salvage rates of >85% in a follow-up of 5 years after operation are reported. This means that about 10% of patients having undergone revascularisation will be exposed to amputation during follow-up [46]. To this group, one must add the small group of patients that are primarily not amenable to angioplasty or bypass surgery.

The ideal treatment in such symptomatic non-reconstructable patients should allow the patient to retain his limb with no or tolerable pain and to maintain a satisfactory level of independence.

The initial use of SCS was for the treatment of chronic, intractable pain of various etiologies. As experience with SCS expanded, other effects such as relief of ischemic pain were recognized. Several European trials have studied the effects of SCS on relief of ischemic pain and microcirculatory blood flow. Success rates of up to 90% for the relief of pain were reported. Microcirculatory parameters have shown significant improvement under stimulation as demonstrated by techniques such as measurement of red blood cell velocity, capillary density, sodium fluorescein appearance time, $TcPO_2$ values, and laser Doppler velocimetry. Moreover, ulcer healing was observed and therefore limb salvage was suggested. These results were followed by an enthusiastic recommendation of SCS for CCLI, and in Europe alone more than 7.000 implants have been performed for vascular indications. However, these studies could not prove the efficacy of SCS due to the lack of a control group.

The effects of SCS on pain are based on the ''Gate Control Theory of Pain'' proposed by Melzack and Wall in 1965 [45]. The inhibitory effects of SCS on the transmission of nociceptive impulses may be exerted segmentally in the spinal cord, at the supraspinal level – or both. The mechanisms discussed vary from blocking of the pain transmission by direct effect on the spinothalamic tracts, activation of descending inhibitory pathways, effects on the sympathetic nervous system, segmental inhibition via coarse fiber activation and brain stem loops, to thalamo-cortical mechanisms. Clinical and experimental evidence does not support the hypothesis of a simple conduction blocking mechanism. Recent studies indicate that an additional mechanism may be involved, the phenomenon of antidromic vasodilation, probably mediated via Aδ-fibers. There is evidence that this effect is mediated by the calcitonin gene-related peptide (CGRP) and that the mechanism is NO dependent. Experimental studies have also demonstrated that neurotransmitters are released in the central nervous system by SCS. Substances of special interest are vasoactive intestinal polypeptide (VIP), serotonin, substance P, noradrenaline, CGRP, gamma-aminobutyric acid (GABA), prostaglandins, nitric oxide (NO), etc.

Reviewing the data of experimental and clinical studies, we can make the following recommendations and conclusions:

1. The selection of patients for SCS is one of the major problems and is closely related to the definition of non-reconstructable CCLI and a study of the skin microcirculation. SCS is only indicated in patients in whom the diagnosis of CCLI is definite and revascularization cannot be performed. Clinical classification according to the European Consensus Document/TASC Document is mandatory but cannot predict the efficacy of SCS. Patients who are most likely to benefit from SCS appear to be those with an ''*intermediate*'' type of skin microcirculation.
2. SCS is effective in the management of ischemic pain. The degree of pain relief among patients suffering from rest pain is higher as compared to patients suffering from ulcers or gangrene. The induction by SCS of paresthesias that cover the foot is an essential prerequisite in order to achieve a good pain relieving effect. Although blind studies are impossible, a placebo effect is conceivable but unlikely because of the sustained benefit of SCS in 70% of the patients and the observation that relief of ischemic pain is lost immediately when there is lead displacement or depletion of the generator.
3. The precise mechanisms to explain the effects of SCS on ischemic pain and microcirculation are still poorly understood. Relief of ischemic pain may be due to blocking of pain signals in the spinal cord, but it seems that pain relief is largely due to a re-established balance between oxygen supply and demand by an increase of microcirculatory blood flow. This effect is most likely mediated by an inhibition of the sympathetically mediated vasoconstriction, but also antidromic vasodilation seems possible.

4. Ischemic ulcers show a definite propensity to heal. Despite this observation, the major randomized trials were not able to show limb salvage by SCS. The European Peripheral Vascular Disease Outcome Study showed that patient selection based on $TcPO_2$ and results of trial screening increase the probability of limb salvage after SCS therapy.
5. Technical complications are rather relatively frequent but of minor severity. In cases of electrode migration, reprogramming of the electrode configuration by the external programmer will often suffice to cover the painful area with paresthesia. Dislodgement or migration of the lead is recognized by a loss or change of the stimulation-produced paresthesia. The average rate of lead breakage is about 7%. Infections, epidural haematoma or spinal fluid leaks are rare.

Conclusions

SCS provides significant long-term pain relief in patients with ischemic pain due to non-reconstructable CCLI and improves ulcer healing owing to effects on the nutritional skin blood flow. Screening by assessement of microcirculation helps predict the remaining reserve capacity likely to be exploited by SCS. SCS in patients with non-reconstructable CCLI provides a significantly better limb salvage compared with conservative treatment modalities if patient selection is based on microcirculatory parameters such as $TcpO_2$.

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Cervical spinal cord stimulation in cerebral ischemia

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Summary

Spinal cord stimulation (SCS) is a well established therapy in the treatment for chronic pain. SCS has also been shown to increase peripheral blood flow and is now an accepted treatment in the management of ischemic limb pain and angina. There is a growing body of evidence that cervical spinal cord stimulation also increases cerebral blood flow (CBF) in both animal and human models. SCS could potentially impact on the treatment of cerebral vasospasm and stroke by an increase in CBF. The utility of SCS is also being explored in novel applications such as adjunctive tumor therapy, where resistance to therapy conferred by tissue hypoxia may be ameliorated by CBF augmentation.

Keywords: Spinal cord stimulation; cerebral ischemia; stroke; hypoxia; cerebral blood flow; vasospasm.

Introduction

Spinal cord stimulation (SCS) was developed following the publication of the ''Gate Theory'' of pain neurotransmission in 1965 [34]. Shealy *et al.* reasoned that the electrical ''gates'' within the dorsal aspect of the spinal cord – postulated by Melzack and Wall – could be artificially stimulated by the use of an extraneous electrical current [48]. The technology of SCS has evolved over the last three decades, but it is essentially unchanged in its underlying concept. Modern-day SCS units consist of an electrical lead, which is implanted over the dorsal dura overlying the spinal cord, and a pulse generator, which delivers a high frequency, low amplitude, square-wave current. While stimulated, patients describe a vibratory sensation in their extremities. This sensation is associated with a significant reduction of pain in the ''stimulated'' extremities. Since its introduction in 1967, SCS has been widely used for the treatment of chronic pain [41, 50]. SCS is generally believed to alter neuronal inputs and activity within the dorsal horn of the spinal cord, thereby reducing the central transmission of pain. Conduction in the dorsal columns has long been thought to be primarily affected by SCS; however, this concept has been challenged [3]. In point of fact, although the efficacy of SCS in the alleviation of pain has been well-established, a great deal of controversy continues to exist regarding its underlying mechanism(s) [50].

A serendipitous discovery by Cook and others using SCS to treat ischemic limb pain in 1976 led to a postulated direct effect on peripheral vascular tone [7]. In this landmark paper, a patient is described in whom painful, ischemic ulcers were observed in the lower extremities. Following the successful application of SCS, the patient's pain was alleviated. In addition, the perfusion to lower extremities improved noticeably and the ischemic ulcers began to heal. When SCS was stopped, the pain and the ulcers reappeared. Re-establishment of SCS once again resulted in improvement in the symptomatic peripheral ischemia.

Since the initial observation, the effects of SCS on vascular tone in the peripheral circulation have been studied extensively in the laboratory [27–29, 37]. Blood flow in the rat hindpaw has been shown to rise dramatically in response to stimulation of the lumbar spinal cord [27]. Both chemical and surgical sympathectomy blunted the vascular response to SCS [27, 28]. Finally, SCS-induced blood flow changes were noted to occur despite transection of the rostral spinal cord or the dorsal nerve roots [27]. These lines of experimental evidence suggest that SCS reduces peripheral sympathetic tone, thereby augmenting blood flow in the limbs [29].

The therapeutic efficacy of SCS in the management of ischemic limb pain is now accepted [24, 26]. It has also been suggested that SCS may reduce ischemic tissue

injury in patients with peripheral vascular disease, although the data supporting this conclusion are mixed [24, 26]. Currently, application of SCS for symptomatic peripheral ischemia constitutes one of the most common indications for SCS in Europe [44].

In addition to its use in peripheral vascular disease, SCS has been reported to be successful in reducing pain from myocardial ischemia. Far from masking incipient myocardial infarction, SCS has been demonstrated to be accompanied by improvement in coronary perfusion and inotropic performance in a multicenter, randomized, prospective trial [30]. Furthermore, analysis of the data from this trial found that both coronary artery bypass grafting and SCS conferred similar protection from anginal episodes and myocardial infarction over a 5-year period [10]. When considered in aggregate, these observations indicate that SCS has a clinically significant vasodilatory effect in peripheral vasculature and may even improve blood flow to ischemic tissue.

Since peripheral vasodilation has been shown to occur with SCS, it was only natural to inquire whether the same effect occurs centrally. Changes in cerebral blood flow related to SCS were the subject of an anecdotal report involving a small number of patients undergoing stimulation for treatment of chronic pain [18]. Hosobuchi and others found that high cervical SCS increased CBF, although the extent of this augmentation and the underlying mechanisms have not been clearly defined [2, 18, 22, 33]. The possibility that CBF may be augmented with SCS has prompted scattered attempts to use SCS in the treatment of cerebral ischemia [2]. Although rather poorly controlled, these reports suggest that cerebral blood flow can be improved in a meaningful way in patients with cerebral ischemia.

Animal models

Several investigators have applied SCS in animal models of cerebral ischemia or physiological preparations designed for measurement of CBF [2, 12, 22, 33, 56]. In goats and dogs, Garcia-March and colleagues found that electrical stimulation at the C2 spinal segment increased CBF by 55% when measured by laser-Doppler flowmetry and by 35% when studied quantitatively by iodoantipyrene autoradiography [12]. Visocchi and co-workers showed that CBF in rabbits will be increased by cervical SCS but can be attenuated by concurrent stimulation of the sympathetic trunk [56]. Using a cat model, Isono and colleagues found that CBF changes occurred only with SCS performed in the cervical spine [22]. Moreover, these authors discovered that sectioning of the dorsal columns at the cervicomedullary junction abolished CBF changes. These findings have been corroborated independently in our laboratory using a rat model of focal cerebral ischemia [46].

The rat model has been successfully applied to the study of the vascular effects of spinal cord stimulation [27–29]. We have adapted this technique in the rat in our laboratory for study of cerebral blood flow. Application of a small current (1 mA, 50 Hz, 200 μsec) results in a significant rise in laser Doppler flow (LDF) (Fig. 1). Quantitative measures of CBF changes with SCS sug-

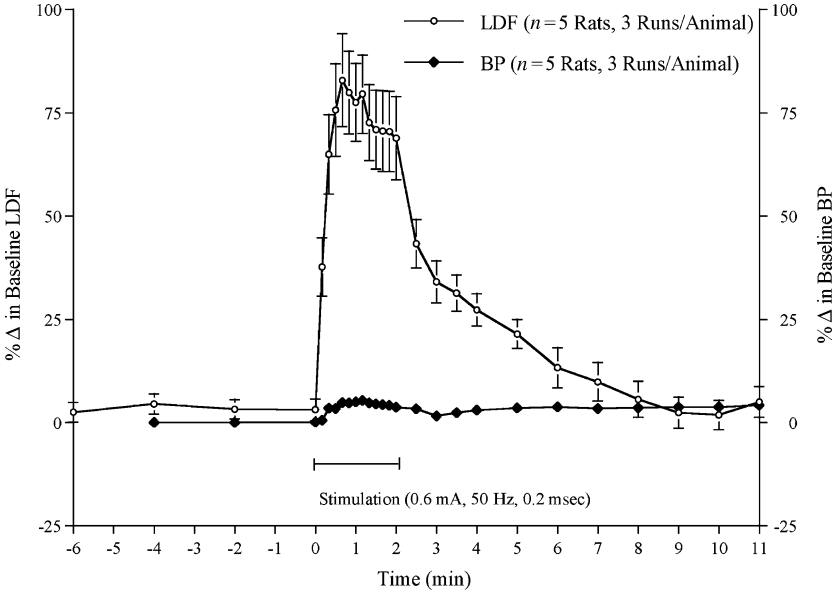


Fig. 1. Cervical SCS increases LDF values. The increase in LDF values is substantial, and lasts for several minutes following the cessation of stimulation. Systemic BP rises slightly with SCS as well. Values are means ± SE ($n = 5$, 3 runs/animal)

Table 1. *CBF changes in spinal cord stimulation*

	CBF (ml/100 gm/min)		
	Control	SCS	%Δ
Anterior cortex	80.2 ± 2.7	120.8 ± 12.0*	50.7
Posterior cortex	72.9 ± 3.9	106.7 ± 8.8*	46.5
Basal ganglia	120.2 ± 5.3	167.3 ± 10.2*	39.2
Cerebellum	139.7 ± 3.1	182.7 ± 10.1*	30.8
Brainstem	183.2 ± 8.1	219.5 ± 8.7*	19.8

*$p < 0.05$ when compared to pre-stimulation values, $n = 5$ rats. Values expressed as mean ± SEM.

gest that this effect is robust, and global (Table 1). The changes in CBF are accompanied by small increases in systemic blood pressure, and appear to slowly resolve over approximately 5–10 minutes following the cessation of stimulation.

One of the principal mechanisms thought to be involved in the vascular effects of SCS is sympathetic activity modulation. There is experimental evidence to this effect in the *peripheral* vascular effects of SCS [27–29]. Using more specific blockade of adrenoreceptor subtypes, we have studied the roles of α_1, α_2, and β receptors in the SCS effect on CBF. Our findings suggest that augmentation of CBF resulting from SCS is significantly mediated by α_1 modulation (Fig. 2). We have

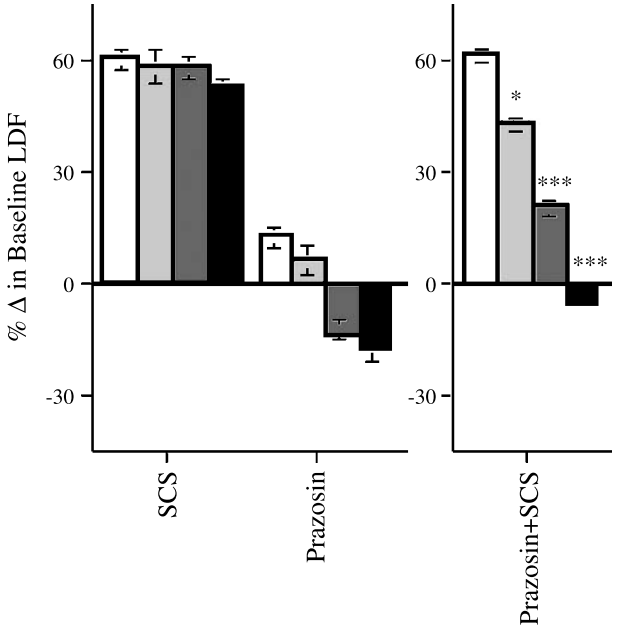


Fig. 2. Prazosin blocks SCS-induced CBF augmentation. Alpha-1 blockade with increasing doses of prazosin significantly attenuated the CBF effects of SCS, indicating that α_1 receptor activity is important in the cerebrovascular actions of SCS. Values are means ± SE ($n = 8$), *$P < 0.05$, ***$P < 0.001$ *vs.* control. □ Control, ▒ Prazosin 0.25 mg/kg, ▓ Prazosin 0.5 mg/kg, ■ Prazosin 1 mg/kg

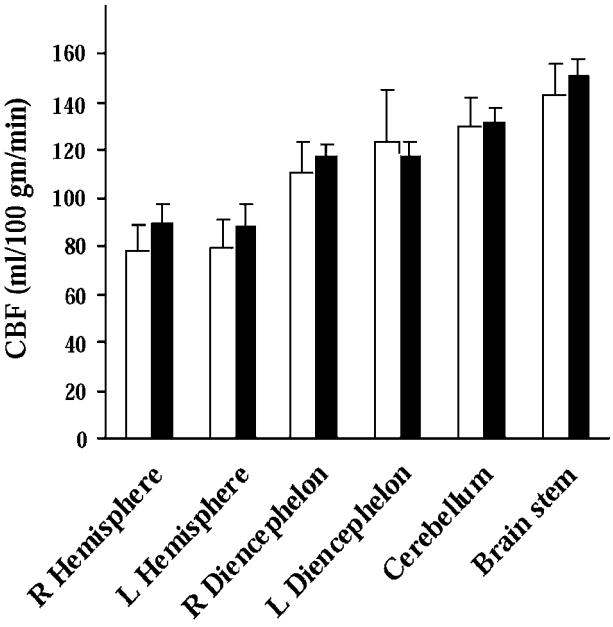
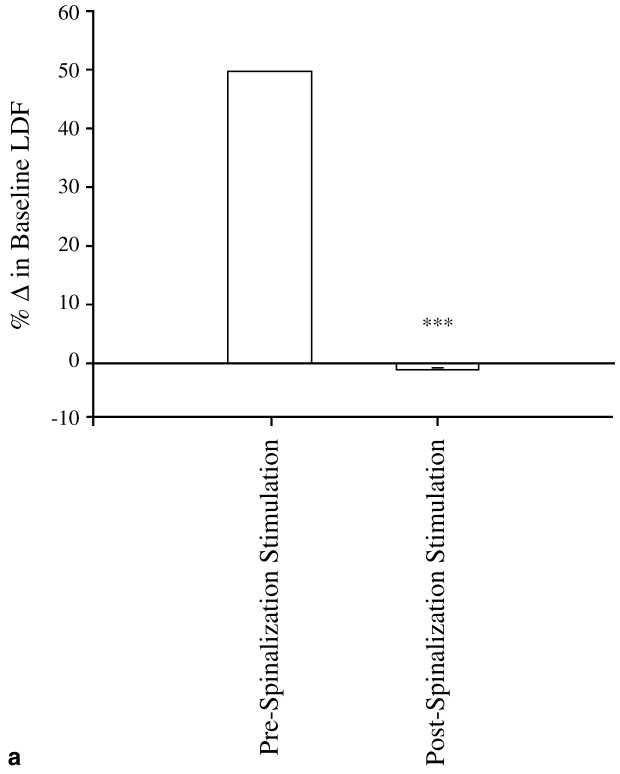


Fig. 3. Surgical sympathectomy does not impair SCS-induced CBF augmentation. Resection of the superior cervical ganglion (*SCG*) was performed bilaterally, without significant effect on the subsequent ability of SCS to increase CBF, as measured by ^{14}C-IMP radiotracer analysis. Values are means ± SE ($n = 10$), *P* nonsignificant. □ SCS, ■ SCS + SCG

also obtained evidence that this does not seem to be conveyed via the cervical sympathetic chain, but rather directly via supraspinal mechanisms (Figs. 3 and 4).

The application of SCS also appears to result in a dramatic reduction of infarct volume in the setting of focal cerebral ischemia utilizing a rat model of focal cerebral ischemia in our laboratory [47]. We induced permanent, focal cerebral ischemia by using either suture-induced occlusion or direct division of the MCA in Sprague-Dawley rats. Electrical stimulation of the cervical spinal cord was performed during cerebral ischemia. CBF was assessed using both LDF and quantitative radiotracer analysis. SCS stimulation increased LDF values to 31% below original baseline values. SCS in the setting of transcranial and suture-induced middle cerebral artery occlusion significantly reduced stroke volumes as well (Fig. 5).

Vasospasm following aneurysmal subarachnoid hemorrhage (SAH) remains a significant cause of morbidity and mortality. Standard therapies include "triple-H" therapy (hemodilution, hypertension, and hypervolemia), calcium channel blockers, and angioplasty. Ebel *et al.* investigated the likelihood that SCS may reduce vasospasm in a rat model of SAH [9]. Their group found that 48 hours after induced SAH, rats with SCS had significantly enhanced cerebral blood flow. More recently,



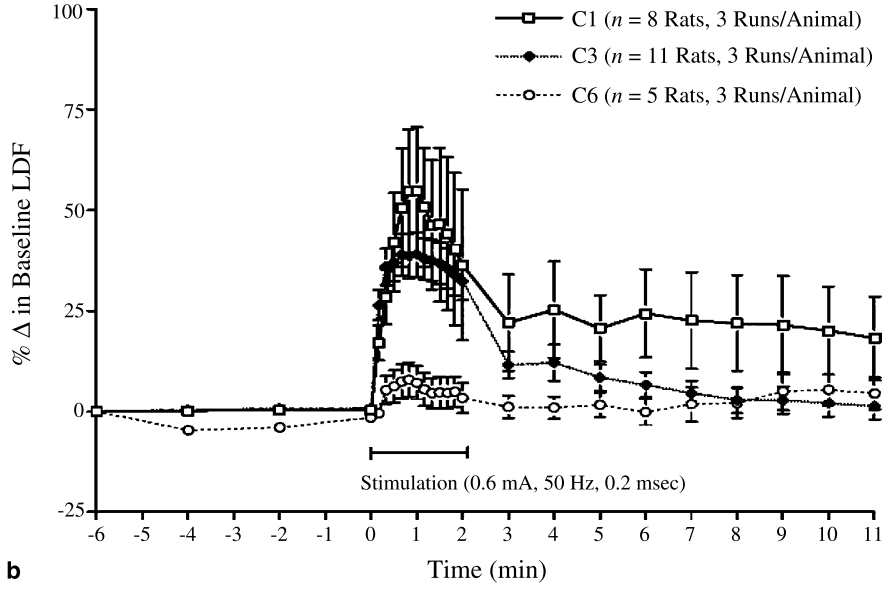


Fig. 4. Cerebrovascular effects of SCS are dependent on transmission of signals rostral to site of stimulation. (a) Complete spinalization of the rat *above* the level of SCS entirely blocks SCS-induced CBF augmentation. This finding is consistent with a supraspinal mechanism, possibly involving activation of vasomotor nuclei in the brainstem. Values are means ± SE ($n = 10$), $^{***}P < 0.001$ *vs.* control. (b) SCS elicits a CBF response which appears to be level-dependent. More rostral stimulation elicits a more robust LDF response in this experimental series. Values are means ± SE ($n = 5$–11)

Karadag *et al.* found that SCS resulted in a significant increase of approximately 30% in CBF in a rabbit model of SAH [25]. Gurelick *et al.* found that in a SAH rabbit model, SCS significantly increased CBF and improved the motor evoked potentials [14].

The experimental evidence accumulated to this point indicates that SCS has the capacity to favorably improve cerebral perfusion and reverse ischemic injury in the brain, perhaps by alterations in sympathetic tone as well as indirect activation of brainstem or cerebellar vasomotor centers.

Mechanisms of SCS-induced CBF changes

Central vasomotor regions

Several centers within the brainstem and cerebellum have been identified which, when stimulated elicit pro-

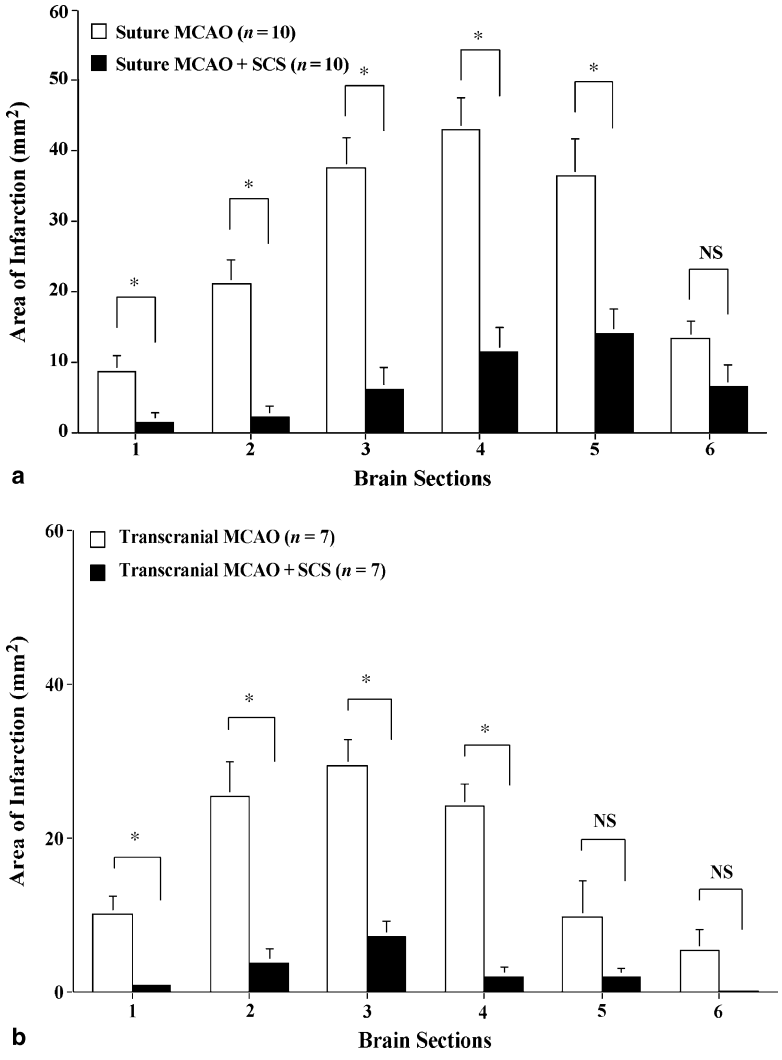


Fig. 5. SCS dramatically reduces stroke area in two models of MCA occlusion in the rat. When focal ischemia was induced by suture occlusion (a) or direct occlusion (b) of the middle cerebral artery in rats, SCS significantly reduced the ensuing stroke injury. Values are means±SE ($n = 7$–10), $^{*}P < 0.05$ *vs.* control

found changes in systemic and regional blood flow. Cardiotonic centers within the brainstem, for example, alter global CBF by changing systemic blood pressure and cardiac performance [8]. In addition, several regions in the brainstem and cerebellum have been described which, when stimulated, elicit profound and widespread changes in CBF. The rostroventrolateral reticular nucleus of the medulla (RVL) and dorsal medullary reticular formation (DMRF) have both been shown to have cerebral vasomotor functions [21, 54]. The fastigial nucleus (FN) in the cerebellum also has this effect, and there is evidence that the medullary and cerebellar centers are part of the same autoregulatory circuit [38]. An intrinsic pathway involving the basal forebrain has been postulated to mediate these global CBF effects [20, 38].

Innervation of cerebral resistance vessels has been demonstrated by both autonomic and somatosensory systems. Sympathetic inputs, arising from the superior cervical ganglion, elicit cerebral vasoconstriction [39, 42]. The trigeminovascular system, originating predominantly from the ophthalmic division of the trigeminal nerve, provides extensive parasympathetic and sensory innervation to pial vasculature; this system elicits vasodilation, and is believed to play a role in vascular headache syndromes [31, 36].

Sympathetic modulation

Alteration of sympathetic tone is thought to underlie the peripheral vascular effects of SCS. In addition, the limited experimental evidence regarding cerebrovascular effects suggests that sympathetic tone may be reduced by stimulation. Administration of ganglionic blockers has been found to attenuate SCS-induced augmentation in CBF response to SCS [56]. The neuroanatomic substrate of this sympathetic modulation remains unknown, however.

Sympathetic efferents, arising from brainstem reticular formation, are located within the ventrolateral aspect of the spinal cord (within the intermediolateral cell column), in a region not readily affected by the dorsal SCS lead. More likely is an indirect modulation of sympathetic tone mediated by collaterals from the dorsal column system into the brainstem reticular formation (e.g. via the RVLM nucleus). It is also possible that sympathetic modulation occurs as a result of modulation of neuronal activity within the dorsal horns of the spinal cord.

Trigeminovascular involvement

Innervation of pial vasculature has been demonstrated to arise from the ophthalmic division of the trigeminal nerve [51, 52]. Stimulation of the nasociliary nerve has been shown to result in ipsilateral cerebrovasodilation [51]. It is possible, therefore, that electrical stimulation of the rostral cervical spinal cord may alter activity within the trigeminal sensory nuclei – resulting in vasodilation mediated by this system. The proximity of the trigeminal sensory nucleus, which may descend a variable distance into the dorsolateral cervical spinal cord, makes this possibility more likely [23, 45]. Still, no experimental evidence for such a mechanism exists. Moreover, changes in CBF due to direct stimulation of the trigeminovascular nerves results in a rather modest increase in CBF [51]. This is in contrast to the more marked changes in CBF seen in response to SCS.

Direct central effects of SCS

It is clear that SCS results in neuronal activation in central somatosensory cortex and relay nuclei. The conscious ''vibratory'' sensation of SCS experienced by patients results from activation of thalamic sensory nuclei and sensory cortex. In addition to activation of primary sensory modalities within the central nervous system, SCS has also been shown to activate association cortex and limbic regions [16].

The central transmission of stimulation in SCS raises the possibility that CBF changes observed in response to SCS are in some way related to activation of central sensory pathways. Direct coupling of regional blood flow in sensory cortex and thalamus would, at the very least, result in regional increases in CBF. It has also been suggested that diffuse thalamocortical projections may account for the global changes in CBF seen in response to SCS [32].

Direct excitation of cortical regions in response to SCS is unlikely to account for SCS-induced CBF changes. Neuronal activity-induced changes in blood flow are tightly coupled to the stimulus, whereas SCS-induced CBF changes have been observed to last long after the cessation of SCS [22]. In addition, the attenuation of the SCS-induced CBF response seen in the presence of sympathetic antagonists is not well-explained with the coupling mechanisms [56]. Finally, the virtual absence of SCS-induced CBF changes with thoracic or lumbar stimulation cannot be explained by a metabolic coupling mechanism [22].

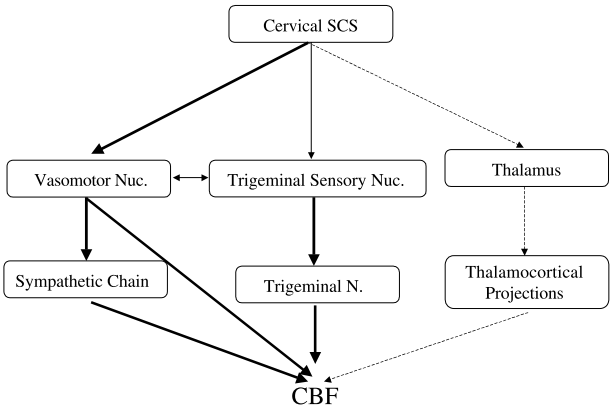


Fig. 6. Schema outlining possible mechanisms underlying cerebrovascular effects of SCS. The thick arrows denote pathways for which there is experimental evidence. Thin arrows denote pathways for which there is no available information. Stippled arrows denote pathways that are not likely to play a role

A proposed model

We hypothesize that stimulation of the cervical spinal cord elicits significant augmentation of global cerebral blood flow through mechanisms that involve alteration in sympathetic tone and stimulation of vasomotor centers within the brainstem and/or cerebellum. It is also possible that activation of the vasodilatory trigeminovascular system has a role in the observed CBF response, although the degree to which this mechanism plays a role is not clear. Direct central excitation and flow-activation coupling is an unlikely mechanism for reasons that have already been outlined. A schema that incorporates these mechanisms is outlined in Fig. 6.

Human data

A number of clinical reports have been published describing the use of SCS in the treatment of cerebral ischemia in patients. These reports have described small numbers of patients and a variety of CBF measurement methods, and have suggested that SCS does indeed augment CBF during ischemia. In 2000, Takanashi *et al.*

Table 2. *Summary of SCS data in cerebral ischemia*

Study	No. of patients	Disease process	CBF measure	Conclusion
Hosobuchi *et al.* [19]	3	symptomatic cerebral ischemia	XeCT, SPECT	increased CBF, extent not specified
Visocchi *et al.* [55]	1	stroke	TCD	43% (contralateral) to 130% (ipsilateral) increase in MCA flow velocity
Broseta *et al.* [2]	10	cerebral low perfusion syndromes	SPECT	increased CBF in penumbral area
Takanashi and Shinonaga [53]	10	cerebral vasospasm	XeCT	CBF in MCA distribution ↑ 20% with SCS
Visocchi *et al.* [57]	18	stroke	TCD, SPECT, NIRS	SPECT: CBF increase in 9/12 patients TCD: velocity increase in 4/11 patients NIRS: CBF increase in 1/1 patients
Shinonaga and Takanashi [49]	12	cerebral vasospasm	XeCT	50% of pts exhibit ↑ in CBF with SCS

published a report on a small series of patients who underwent SCS in the management of cerebral vasospasm following subarachnoid hemorrhage [53]. These patients were studied before SCS and 4 days following its use with Xenon-inhalation CT imaging. The authors reported that regional CBF were stable or slightly increased following the use of SCS despite the fact that CBF normally decreases in patients over this time period. Other series have also shown a beneficial effect of SCS in the setting of cerebral ischemia. Moreover, there were no adverse events related to the use of SCS in the setting of probable cerebral ischemia in any of these studies (Table 2). Although available data on the use of SCS in cerebral ischemia in humans does not suggest that there are significant ill-effects associated with it, its efficacy is difficult to gauge, as the published studies are not designed to address this issue.

Future directions

Stroke remains a significant public health burden in the United States. Currently the FDA has authorized only one clinically effective treatment – tissue plasminogen activator (t-PA). One of the major difficulties with t-PA includes the danger of hemorrhagic conversion and the three hour window in which the therapy must be administered. Given the safety record of SCS and its impact on CBF, SCS may allow for a novel therapy with which to treat ischemic stroke with a potentially decreased risk of hemorrhagic conversion and a longer time window for intervention. This potential is currently being explored in clinical trial.

The use of SCS as an adjunct in the treatment of brain tumors represents a novel application of the technology to a new group of patients. A common characteristic of across of broad spectrum malignancies, including brain tumors, is tissue hypoxia [6, 15, 43]. Tumor hypoxia can contribute to both radiation and chemotherapeutic resistance as many therapies require adequate oxygen tension to have maximal cytotoxic effects. Additionally, low tumor oxygen tension can promote resistance through induction of gene expression, modulation of gene expression, changes in cellular metabolism, and selective pressure for apoptosis resistant cell populations thereby encouraging tumor spread [35]. Brizel *et al.* demonstrated that tumor hypoxia adversely impacted the prognosis of patients with head and neck cancer [1]. Other groups have demonstrated similar findings in patients with head and neck cancer and cervical cancer [11, 13, 17, 40].

Clavo *et al.* has published research on a novel use of SCS in the treatment of brain tumors by addressing the issue of tissue hypoxia [4, 5]. They studied the effect of SCS on regional blood flow in patients with high-grade brain tumors (Grade III, IV). Fifteen patients had SCS implanted prior to beginning radiotherapy. They found that 75% of patients had a 15% increase in tumor blood flow ($p = 0.033$). Additionally they noted an increase of 18% in systolic and diastolic MCA blood flow velocities ($p < 0.002$) and an increase of 60% in blood flow through the common carotid artery ($p < 0.013$). The increase in tumor blood flow may allow for increase drug delivery to the tumor and could be utilized as an adjunct to chemotherapy or radiation.

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Spinal cord stimulation in the treatment of post-stroke patients: current state and future directions

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Summary

A decrease in cerebral blood flow (CBF) and brain metabolic activity are well-known complications of stroke. Spinal cord stimulation (SCS) is successfully being used for the treatment of several low-perfusion syndromes. The aim of this chapter is to describe the data that support the effect of SCS on CBF and the use of SCS in the treatment of stroke and cerebral low perfusion syndromes. In addition, we present our relevant studies. Since April 1995, we have assessed 49 non-stroke patients. The following parameters were measured pre- and post-stroke: 1) CBF in healthy contralateral tissue by single photon emission computed tomography (SPECT), 2) systolic and diastolic velocity in the middle cerebral artery (MCA) by transcranial Doppler, 3) blood flow quantification in the common carotid artery (CCA) by color Doppler, and 4) glucose metabolism in healthy contralateral tissue by positron emission tomography (PET). Our results showed that during cervical SCS there was a significant ($p < 0.001$) increase in systolic ($\geq$21%) and diastolic (>26%) velocity in the MCA, and CCA blood flow ($\geq$51%) as well as glucose metabolism (44%). We concluded that cervical SCS (cSCS) can modify CBF and brain metabolism. Its potential role in the management of stroke and low-perfusion syndromes is further investigated by experimental studies and reports describing clinical experience. Appropriate clinical trials are warranted.

Keywords: Cerebral blood flow; color Doppler; low-perfusion syndromes; metabolism; neuromodulation; PET; SPECT; spinal cord stimulation; stroke; transcranial Doppler.

Introduction

Stroke has significant clinical and social repercussions. Analyses of the latest data from the USA indicated that in the year 2002, stroke was the 3rd leading cause of death (162,672 people). The prevalence was 2.6% (5,400,000 patients) and about 700,000 people had *de novo* stroke or recurrence of the disease; approximately 500,000 and 200,000 respectively. The estimated cost was 56.8 billion dollars [1].

In 80% of patients, stroke is mediated by an ischemic process with local decrease of cerebral blood flow (CBF) and of metabolic activity in the brain. There is rapid loss of function in the ischemic brain tissue. However, considerable lesional and/or peri-lesional areas (termed ''ischemic penumbra'') can retain viability for many hours. One of the main objectives of stroke research is to recover this ischemic penumbra and to pre-empt its progression towards nonviable brain tissue. The basis of stroke management to date has been merely to maintain appropriate blood pressure control so as to guarantee CBF and to avoid complications and morbidity. Only a few specific treatments such as aspirin have shown limited but consistent benefit in preventing new attacks [22], while anti-thrombolytic treatment with recombinant tissue plasminogen activator rt-PA have been somewhat successful if applied within the first 3 hours of the episode, and only in selected patients [8].

Spinal cord stimulation (SCS) has been used successfully for the treatment of ischemic syndromes such as vasospasm [16], peripheral vascular disease [2], and angina pectoris [9]. However, studies on SCS in CBF disorder are limited; most studies have been performed in patients without CBF diseases. In this chapter, we summarize 1) the data supporting CBF modification using SCS; 2) our studies of CBF improvement using SCS technique; 3) animal studies using SCS in cerebral low-perfusion syndromes; 4) the limited clinical

experiences using SCS in patients with cerebral low-perfusion syndromes.

Data supporting the modification of CBF using SCS

Twenty years ago, Hosobuchi *et al.*, using the 133-Xenon washout technique, described that CBF could be increased by SCS with electrodes implanted at the cervical level for the treatment of pain [11]. Since then, the effects of SCS on CBF have been well documented by various methods in different studies. In 1989, using laser Doppler flowmetry, studies on dogs and goats showed an increase of >50% in CBF in the common and internal carotid arteries following cervical SCS [7]. Also in 1989, there was a case report on a vegetative patient in whom cSCS had been applied. This report showed that following cSCS the pattern of CBF increase as assessed by single photon emission computed tomography (SPECT) was similar to the increase of the cerebral metabolic rate according to glucose uptake measured by positron emission tomography (PET) [15]. In 1991, a study described that SCS increases CBF in humans by using two different techniques: 133-Xenon washout and trans-cranial Doppler (TCD). Furthermore, a potential competitive effect between CO_2 and SCS upon the mechanisms of CBF regulation was postulated [14]. In 1997, Hautvast described blood flow increases measured by PET in specific areas of brainstem and thalamus in patients undergoing SCS at the upper thoracic level (T1 level) for the treatment of angina pectoris [10]. Using laser Doppler flowmetry and radiotracer studies, Sagher and co-workers described that SCS-induced CBF increases in rats. They also postulated a role of the brainstem vasomotor center and sympathetic tone in the vascular effects of cSCS [20] and proposed the pulse width and frequency of the stimulation to be applied for optimal cerebrovascular response [25].

Effects of cSCS on cerebral blood flow and metabolism: experience of the Las Palmas team

Historically, our studies on CBF had been conducted in non-stroke patients. However, in the last 10 years our multidisciplinary group has assessed the effect of cSCS on several cerebral parameters. Between April 1995 and December 2004, we evaluated 49 patients: 6 non-cancer patients with paraesthesia and/or chronic pain (only Doppler measurements), 15 with advanced head and neck cancer, and 28 with previous diagnosis of malignant brain tumors. We have described the specific effects of cSCS on brain tumor tissue and their potential implications in another chapter of this supplement which deals with the pathophysiology and blood flow alterations in high-grade gliomas. Tumors and malignant gliomas are different from stroke and are usually characterized by local and regional ischemia and hypoxia; parameters that can be modified by cSCS. In the present article, we summarize data related with non-tumor tissue. The techniques used and our results are presented in chronological order according to the time of introduction of the techniques in our protocols for the assessment of patients.

Between April 1995 and February 1999, CBF in tumor and healthy cerebral areas were assessed by ^{99}Tc-HMPAO-SPECT using 2 different devices: a Siemens Orbiter tomocamera (Insular University Hospital, Las Palmas) and an Elscint Helix double-head 75 tomocamera (DIMEC Center). SPECT indices were obtained pre- and post-cSCS in 12 patients. We observed a significant blood flow increase in brain tumor tissues (see specific chapter for more details). However, we did not notice significant blood flow changes in healthy contra-lateral brain tissues [4]. One of the potential explanations is that SPECT is a semi-quantitative method. In our studies, the SPECT index reflected the ratio between the different brain areas and the cerebellum, the area in which the CBF increase was greater following cSCS [3]. Hence, a real increase in brain tissue perfusion would not be observed if it was lower than the increase in cerebellum. An altered response to cSCS, secondary to the presence of tumor or previous resection, could also be an explanation although this was not well supported by our subsequent studies.

Between June 1995 and February 1999, velocimetry (cm/s) in the middle cerebral artery (MCA) was assessed by TCD in the trans-temporal approach, using a 2 MHz probe from an Angiodine-2 Fluo-Link 300® device (DMS; Montpellier, France). Bilateral systolic and diastolic velocities were obtained in 32 patients in basal condition as well as between 1 and 10 min post-cSCS. It was not possible to locate an ultrasonic window in 3 of the 35 patients. The results indicated bilateral statistically significant increase in systolic velocity (≥21%) and diastolic velocity (≥26%) in this group of patients ($p < 0.001$) [17] (Figs. 1 and 2). Our results agree with previous TCD studies by other authors [14]. If we assume that the diameter of the MCA remained unchanged over the short time-course of the study, the higher velocities would be related to a higher blood flow. However, we must take into account that TCD is a semi-quantita-

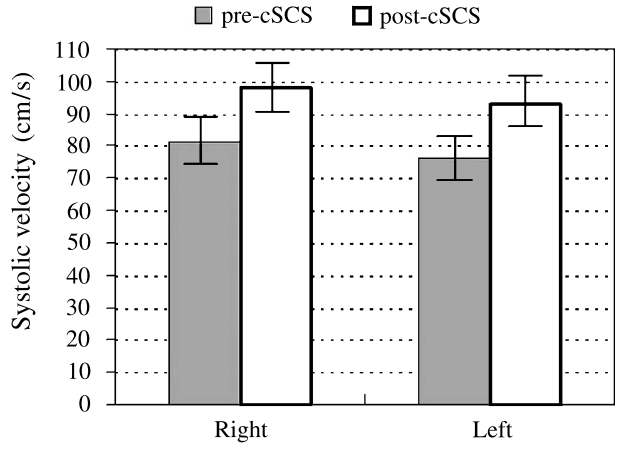

Fig. 1. Systolic velocity in middle cerebral arteries (MCA). During cSCS, systolic velocity in MCA increased bilaterally ≥21% ($p < 0.001$). The measurements were done with trans-cranial Doppler. Error bars show the 95% confidence intervals [17]

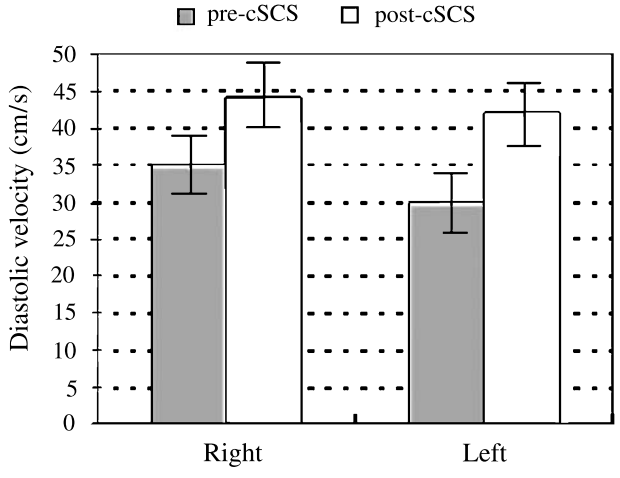

Fig. 2. Diastolic velocity in middle cerebral arteries (MCA). During cSCS, diastolic velocity in MCA increased bilaterally ≥26% ($p < 0.001$). The measurements were done with trans-cranial Doppler. Error bars show the 95% confidence intervals [17]

tive technique which measures velocity (cm/s), and this could be increased by a decrease in vessel diameter despite a decrease in blood flow.

Between March 1996 and February 1999, we evaluated blood flow (ml/min) in the common carotid artery (CCA) using color Doppler quantification with a 7 MHz probe attached to a Philips-Ultrasound P-800 unit® (Philips Ultrasound DR5312 P-SD-800, California). Bilateral mean blood flow was measured in 27 patients pre-cSCS, and between 1 and 10 min post-cSCS. The results indicated bilateral statistically significant increase in the mean blood flow in CCA (≥51%) in this group of patients ($p < 0.001$) [17] (Fig. 3). This is a quantitative

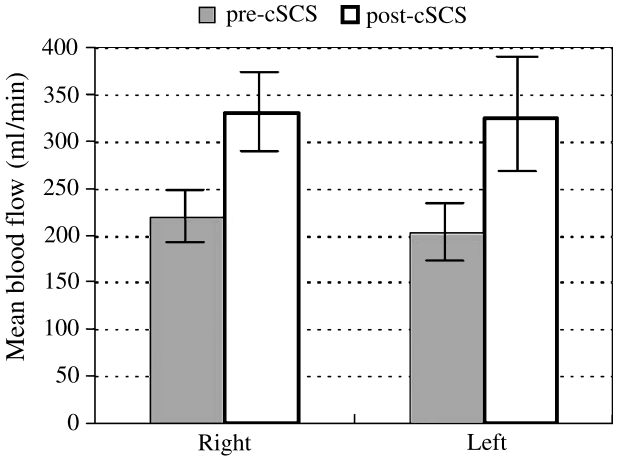

Fig. 3. Mean blood flow in common carotid arteries (CCA). During cSCS, mean blood flow increased in CCA bilaterally >50% ($p < 0.001$). The measurements were done by using color Doppler. Error bars show the 95% confidence intervals [17]

technique that directly evaluates blood flow in ml/min and provides an indisputable indication of blood flow increase in CCA. In addition, the high magnitude of the effect is concordant with experimental data reported by other authors [7]. However, the site of assessment is outside the brain and the intracranial blood flow and hence is not affected by its sophisticated self-regulation. An increased blood flow in CCA does not imply an increase in CBF.

Between March 2000 and December 2004, we measured cerebral glucose metabolism using the technique of 18-fluoro-2-deoxyglucose-PET (^{18}FDG-PET) via a C-PET 250 device (Philips-ADAC-UGM, Philadelphia, USA). The measurements were performed at the FOCUSCAN PET Center (Madrid, Spain). There were 14 patients evaluated for possible relapse and/or new brain tumor. Following the basal PET study, the cSCS device was connected for 10 min before i.v. injection of the second ^{18}FDG dose. The stimulus device remained switched on for the next 20–30 min which means stimulation was switched off about 20 min after the injection and before the second ^{18}FDG-PET scan. The maximum standardized uptake values (SUV_{max}) were calculated in both PET studies in pathological and healthy contralateral brain tissue. In 11 patients who had macroscopically evident tumor tissue, glucose metabolism in tumor and peri-tumoral areas was significantly increased, similar to what has already been described in our article on cSCS and brain tumors [5]. The glucose metabolism results in healthy contra-lateral brain tissue were also quite noteworthy. The PET studies during cSCS showed signifi-

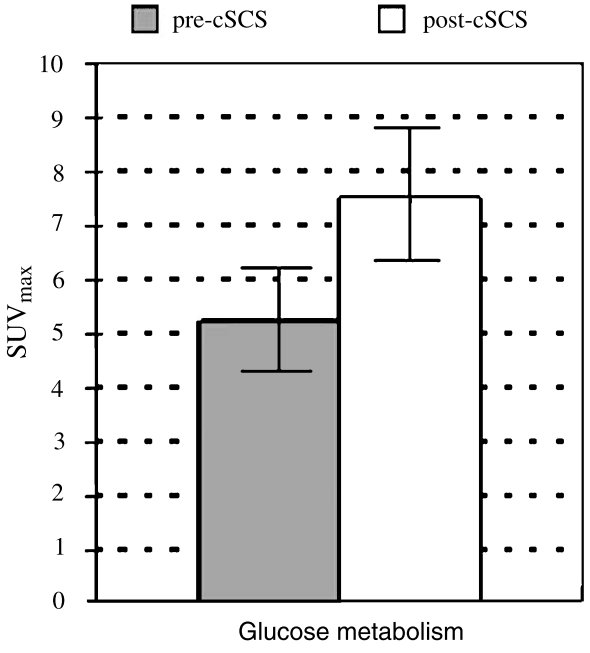

Fig. 4. Glucose metabolism in healthy brain tissue. During cSCS, glucose metabolism (expressed as the maximum standardized uptake values; SUV_{max}) in the healthy cerebral hemisphere increased by 44% ($p < 0.001$). The measurements were done by positron emission tomography (PET). Error bars show the 95% confidence intervals. The estimated maximal residual contribution (carry-over) from the first to the second PET studies was estimated as <17.1% [18]

cant increase in ^{18}FDG uptake (mean 44%) in healthy brain tissue ($p < 0.001$). The "maximal-residual-activity" of the first ^{18}FDG dose that, potentially, could have contributed to this increase in activity in the second PET-scan was estimated as $\leq$17.1% [18] (Fig. 4). Hence, if we adjust the observed percentage increase for this potential maximal carry-over, a more realistic estimate of the increase would be around 27%. Since glucose supply depends on blood flow, our hypothesis is that the increase in glucose uptake in healthy brain tissue after cSCS would be associated with increased glucose availability secondary to an improved CBF, an aspect of SCS that we have documented in this chapter. However, the sequence of events could be questioned i.e. which happens first: the increase in blood flow or the neuronal activation and increase in glucose metabolism? Whichever the explanation, blood flow and glucose metabolism appear to be related in brain tissue and both are altered simultaneously in stroke and other cerebral low-perfusion syndromes. Further support for the increase in both parameters following cSCS was provided by the study mentioned earlier [15], in which simultaneous assessments by SPECT and PET had been conducted.

Animal studies using SCS in cerebral low-perfusion syndromes

Experimental studies using animal models of cerebrovascular disease support the effectiveness of SCS. The effects of SCS in the middle cerebral artery occlusion model for stroke were explored in cats [13] and rats [21]. Both studies found a significant decrease in infarct volume while the Matsui *et al.* study also demonstrated a 56% prolongation of survival [13].

In 1994, rabbits were used to study the effect of cSCS in 3 models of brain infarct (bilateral carotid ligation, microcoagulation of the unilateral MCA or of the vertebral artery). cSCS was performed one week after infarct induction and the authors [3] observed a 27% increase in CBF and a 32% increase in the flow in the posterior fossa. Several studies have evaluated the effect of SCS in rat models of sub-arachnoid hemorrhage. Using SPECT, it was shown that rats receiving cSCS were protected against decreased CBF induced by sub-arachnoid hemorrhage [6]. Since vaso-constriction subsequent to sub-arachnoid hemorrhage is mediated by the sympathetic nervous system, the reduction in sympathetic tone would play an important role in the cSCS mechanism-of-action.

Clinical experiences using SCS in patients with cerebral low perfusion syndromes

The potential role of SCS in the management of low-perfusion syndromes is supported by clinical experiences; albeit limited. In 1985, Hosobuchi [11] highlighted the potential efficacy of SCS in the treatment of decreased CBF syndromes. Some years later, using Xenon studies or SPECT, he described the CBF increase during cSCS and symptom improvement of cerebral ischemia in 3 patients [12]. In 1994, a study in 10 patients with various cerebral low-perfusion syndromes, using SPECT, demonstrated that an increase in blood flow in the penumbral perilesional area was combined with a trend towards improvement in clinical symptoms [3]. In 1994, Visocchi *et al.* described a patient with spastic hemiparesis secondary to an ischemic stroke. The administration of cSCS improved the patient's spasticity, voluntary movements, and CBF as assessed by TCD [23]. Some years later the same group described the effect of SCS on 18 stroke patients. The assessment by TCD, SPECT, and near-infrared-spectroscopy, although not statistically significant, revealed a correlation of clinical and hemodynamic changes (with clinical improvement) and an increase in blood flow parameters, especially those assessed by TCD [24].

Although not involving stroke patients, our recent studies may legitimately be included here. Using ^{18}FDG-PET we have reported a significant improvement in glucose metabolism in radiation-induced brain ischemic tissue after cSCS administration in 6 patients [19]. These results are provisional, but very promising.

Discussion

In a previous review on the potential effects of SCS on stroke, Sagher *et al.* [21] described the mechanisms that could be involved such as the sympathicolytic effect or the modulation of activity in brain centers. Whatever the mechanisms, the improvement on CBF appears to be the main clinical result. There is increasing evidence to support this; experimental studies have described a beneficial effect of SCS in cerebral low-perfusion syndromes and in post-stroke conditions. The clinical experiences, albeit limited, support a potential role of SCS in the clinical management of stroke in humans [3, 12, 24].

Optimal parameters and timing of neurostimulation should be investigated. Pulse width and frequency of the stimulation can have an impact on the magnitude of the cerebrovascular response; the optimal values in rats have been shown to be within the therapeutic range applied in humans [25]. With respect to the timing of SCS, another unresolved question is the maximum interval from the onset of infarct in which SCS should be implemented in order to produce beneficial effects. The experimental animal studies described previously showed a benefit of SCS using very different protocols; for example, commencement of SCS ranging from 1 hour [21] to 1 week [3] post-stroke, and duration of stimulation from 2 min [21] to 2 hours [3]. In a study of experimental subarachnoid hemorrhage, the used parameters were in the middle of the range, and SCS was administered two days later [6]. Other clinical experiences have described the delayed placement of SCS electrodes and the protracted stimulation time. Results indicate that there is a benefit irrespective of when SCS is implemented following infarction. This is very important with regard to standard clinical practice in most institutions because placement of electrode may not be carried out under optimal conditions within the first hours or days of a stroke.

Currently, evidence level for the use of SCS in cerebral low-perfusion syndromes and grade of recommendation are very low, i.e. levels 4–5 and grades C–D, respectively. However, we believe that the potential role of SCS in the management of these syndromes is strongly supported by the existing information which includes: 1) effect of cSCS on CBF and brain metabolism, 2) well conducted experimental studies in animal models; 3) increasing reports of clinical experience. The potential role of SCS in brain ischemic syndromes is also supported by available clinical evidence of the use of SCS in the management of peripheral vascular diseases and ischemic heart disease. Cerebrovascular disease has a high incidence and considerable socio-economic consequences due to limited therapeutic modalities available. Hence, we believe that appropriate, well designed clinical trials should be conducted in order to systematically evaluate whether cSCS can improve key clinical parameters, quality-of-life, and prognosis of either specific clinical conditions, or subgroups of patients, as was described earlier in this article.

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Neurostimulation for refractory angina pectoris

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Summary

Spinal cord stimulation (SCS) has been shown to be particularly useful, safe and effective treatment in the management of patients with refractory angina pectoris and those unsuitable for percutaneous or surgical revascularisation. Clinical and experimental research has shown that it decreases myocardial ischemia without masking the clinical symptoms of its imminent development. In addition to providing pain relief, neurostimulation has also been shown to improve microcirculatory blood flow and increase the myocardial threshold for ischaemia. The anti-ischaemic effects of SCS have been evaluated by: a) exercise testing, b) ambulatory electrocardiogram (ECG), and c) invasive measurements of lactate from coronary sinus blood samples. Patients have reported not only significantly fewer angina attacks but also decreased consumption of glyceryl trinitrate and improved quality of life. A number of mechanisms have been proposed including placebo effects, primary anti-nociceptive effects, involvement of endogenous opiates, anti-sympathetic nervous system effects, increases in coronary blood flow, and redistribution of myocardial blood flow.

Keywords: Coronary artery disease; neuro-stimulation; refractory angina pectoris; spinal cord stimulation; myocardial ischaemia.

Introduction

Spinal cord neuromodulation owes its origin to the gate theory of pain proposed by Melzack and Wall [28]. On the basis of this theory, it was predicted that stimulation of visceral afferent nerves would reduce or block the transmission of pain-related signals relaying through the spinal cord. The nociceptive unmyelinated C and A delta afferent fibres are inhibited by nonnociceptive myelinated afferent fibres [4, 47]. The potential anti-ischaemic properties of neurostimulation provoked interest in the possibility of treating coronary artery insufficiency; spinal cord stimulation (SCS) was shown to be a treatment option for patients with advanced coronary disease who are unsuitable or refractory to percutaneous or surgical revascularisation techniques. The first reports on the use of transcutaneous electrical nerve stimulation (TENS) for chronic angina pectoris appeared in 1982 [29]. The first stimulator for intractable angina was implanted in 1987 [37]. These patients were severely disabled due to inoperable multi-vessel cardiac disease with chest discomfort during minimal exercise despite maximal anti-anginal drug therapy. In order to consider a patient for SCS all pharmaceutical treatments should first be exploited. Such drug therapy should consist of at least two drugs of a list including beta blockers, calcium antagonists or long acting nitrates.

Neuromodulation and angina

The occurrence of an episode of anginal pain may be experienced as a life threatening condition by the patient. The neurophysiological pathway of angina pectoris begins at the level of cardiac sensory receptors which are activated by chemical and mechanical stimuli. The most frequent noxious insults are caused by ischaemia. The afferent transmission of painful messages converges with many other sympathetic afferents of the same dermotome, on the same dorsal horn spinal neuron. The further transmission of impulses towards the thalamus is modulated by other spinal centres and peripheral or descending stimuli. Final pain perception occurs in the cortex and is influenced by the psycho-social background of each patient. The perception of angina pectoris is associated with increased regional cerebral blood flow in the hypothalamus, periaqueductal grey matter, lateral prefrontal cortex and left inferior anterocaudal cingulate cortex. The increased flow bilaterally in the thalamus suggests a gate function for afferent pain signals [1].

Several chemical mediators in the perception and modulation of pain have been recognised [2]. These include

bradykinin and prostaglandins which are released by the ischaemic myocardium and contribute to the initial excitation of the nociceptive afferent nerve endings. Endogenous opioids such as endorphin, encephalin and dysmorphins have also been implicated in the central modulation of pain [3]. The modulation of cardiac afferent impulses in the dorsal horn has also been investigated. Research has demonstrated a lowering of the anginal threshold by oesophageal stimulation during exercise and, on the other hand, a rise of the anginal threshold by TENS, SCS or carotid sinus stimulation [9].

Indications

Although several coronary pain patterns have been identified in both stable and unstable angina, the group of patients who have been found particularly suitable for spinal cord stimulation are those suffering from refractory angina pectoris [6]. This is a group of patients with stable chronic angina pectoris with intermittent periods of unstable angina. This group has either severe coronary artery disease without any realistic treatment option by a revascularisation procedure or angiographically normal coronary arteries. In such patients, anginal complaints may be difficult to alleviate with conventional management. These patients are refractory to the standard therapeutic measures and, therefore, suffer from intractable angina. The patients who are considered as candidates for treatment of intractable angina pectoris by SCS require careful screening. It is important to ensure that the chest pain is due to true reversible myocardial ischemia and that the patients will be fully cooperative throughout this treatment. Ideal patients are those with severe angina pectoris (New York Heart Association Classes III and IV) [48], who are considered either refractory to medical therapy or not suitable for open heart surgery. In such patients, revascularisation of the myocardium with coronary artery bypass grafting and/or percutaneous transluminal coronary angioplasty either were found not suitable or failed and the patients continue to experience disabling intractable angina in spite of maximal pharmacological therapy [31]. Consequently, refractory angina becomes in many cases a daily occurrence dominating their lives, and often making it impossible to perform even simple activities of daily living that most of people take for granted [41]. Such patients make frequent visits to the hospital for treatment of their angina. This is associated with a financial burden, not only to the patients both also to the health care system [37].

Mechanism of action

Many pathophysiological theories have been proposed, but the exact mechanism is still not known [11–13, 36].

Placebo effect

This is usually unrelated to any physiological action and it is rather a response to the psychological effect of any form of intervention [27]. This effect is estimated to contribute up to 30–40% to the initial benefit in any medical treatment, but it decreases with time, and usually any placebo effect is negligible after 2–3 months [25, 49].

Anti-nociceptive gating effect

Since SCS was started on the basis of the gate theory of pain, the primary aim was to block the transmission of pain by producing a counter-stimulation [38]. This has been met by resistance from many clinicians who oppose the use of neurostimulation in angina pectoris. It has been argued that the block of transmission of painful stimuli by SCS could deprive patients of an important warning signal. The anti ischaemic effect seen in peripheral vascular disease has not been taken into account. The phenomenon of myocardial ischaemia develops in cycles as the pain and the distress lead to general and segmental increase in sympathetic nervous system activity and an increase of the oxygen demand of the myocardium. Thus, by alleviating pain and breaking this cycle, myocardial ischaemia is alleviated, the angina attack decreases in intensity and a fall of the total ischaemic burden follows. There is a shift in ischaemic threshold with no ''masking of symptoms''. Instead, the same symptoms appear at a higher level of exertion and remain consistent with the lactate production [32].

Endongenous opiates

Beta-endorphins are known to be released during SCS in patients with angina [13]. They act by antagonising sympathetic stimulation, thus reducing contractility and oxygen consumption by the myocardium. This is mainly the reason why opiates are widely used to treat acute ischaemic pain and intrathecal opiates have been recommended to treat refractory angina [39].

Increase of coronary blood flow

Neurostimulation leads to an increase of oxygen delivery at the microcirculatory level and possibly an

increase in coronary blood flow as well [10, 30, 31]. Although studies have demonstrated that TENS produces an increase in coronary blood flow at rest in patients suffering from either angina or syndrome X, this effect has not been demonstrated in patients implanted with a spinal cord stimulator [33, 34].

Anti-sympathetic effect

The neurostimulation acts in a similar manner to drugs blocking the Beta adrenoreceptors leading to decreased oxygen consumption. The modest fall in the systolic blood pressure observed during SCS, the relevant effect of cervical sympathectomy in intractable angina (i.e. an increase in the ischaemic threshold), and the beneficial vasomotor effects of anti-sympathetic mechanisms offer support to the existence of a correlation between SCS and a potential anti-sympathetic mode of action [50].

Myocardial perfusion and redistribution of coronary blood flow

Ischaemic threshold in angina patients is increased in consequence to the decrease in myocardial oxygen consumption in patients treated by SCS. SCS is known to act as an adenosine antagonist [16, 43, 46] and has a theophylline-like effect, i.e. blocks adenosine-mediated intramural and subendocardial blood steal phenomena. In this process, blood is redistributed from non-ischaemic areas to the ischaemic ones, a phenomenon called the 'Robin Hood Effect'.

Procedure

Prior to implantation, it is essential that not only the medical team but also the patient and his carer have a clear understanding of the goals and objectives of the treatment.

The placement of SCS electrode requires the patients' feedback. Therefore, it is important that the patient is placed in a comfortable position that minimises the need for adjunctive intravenous narcotics or sedation. With the patient in the prone position and under fluoroscopy the dorsal epidural space is punctured either transcutaneously or through an open neurosurgical laminotomy by a midline or lateral approach usually at the 4th–5th thoracic vertebra level. A thin or flat multi-polar electrode is introduced to the site where it is expected to produce adequate paraesthesias and then manipulated further while the stimulation is applied. Slight displacement of the electrode by only 1–2 mm may influence the efficacy of stimulation. The electrode is advanced in the midline in a cephalad direction under fluoroscopic guidance to the C6-T1 position; this allows coverage of the anatomic distribution of pain without uncomfortable segmental or radicular effect. The electrode is attached to the pulse generator via a sterile screening cable. In many centres, the temporary placement of the percutaneous epidural electrode is a routine screening procedure prior to permanent electrode placement. Trial stimulation is carried out with the patient awake and able to describe the type and location of the stimulation and its effect on the pain. When tunnelling the electrode, a straight line should be followed to minimize the possibility of subcutaneous electrode kinking and breakage. The extension set is connected to the implantable pulse generator (IPG) and repeat trial stimulation is carried out to verify that the patient still perceives an acceptable stimulation. Over a three day period, extensive testing and assessments take place [33]. If the patient reports at least 50% pain relief while demonstrating stable or increased level of activity with stable or decreased level of pain medication, the decision to proceed and implant a permanent stimulator is made. Therefore, in a patient in whom the Stage 1 trial of SCS has been successful, it is sensible to proceed with a Stage 2 permanent implantation of the IPG.

Stage 2 involves taking the patient back to the operating theatre. After the extension set is removed, an incision in the anterior subcostal region is made and a subcutaneous pocket is created large enough to accommodate the pulse generator. A new, sterile implantable extension electrode is attached to the tunnelling device, which is then drawn back out of the midline incision. The proximal end of the extension electrode is then connected to the epidural stimulating electrode and the distal end of the extension electrode is connected to the pulse generator. The pulse generator is then activated to verify that the system is working. The stimulation intensity is individualised for each patient to achieve optimal tolerable stimulation. The frequency and pulse rates are standardised at 80 Hz and 230 msec, respectively. The patients are stimulated using a continuous mode. Currently, the majority of doctors prefer to complete the entire procedure at one sitting to reduce cost and infection risk. If the initial table trial is unconvincing, it is reasonable to internalize the trial lead and implant the IPG a few days later. In this respect, the procedure differs from the conventional screening trials in other pain syndromes, where after the electrode is

implanted, the patient undergoes an out-patient trial to determine efficacy. In other types of pain, the IPG is implanted once efficacy has been established. In patients with angina this may be impractical because of episodic character of chest pain. Secondly, the insertion of the electrode must be done under local anaesthesia because intra-operative stimulation is necessary in order to ensure the optimal position of the electrode. This is crucial, because the stimulation paraesthesia must cover the area in which the angina is felt. In addition, one must pay close attention to the perception threshold (amplitude at which the paraesthesia is first felt) and the amplitude at which the stimulation becomes uncomfortable or painful. Ideally, these amplitudes should be as far apart as possible in order to provide a wide range for use of SCS. In most of the studies, the stimulation is performed for a variable period, several times daily and during acute anginal attacks, while is many studies, continuous stimulation is employed. Currently, there is no data comparing the efficacy of intermittent versus continuous stimulation, and it appears that both methods are effective.

Complications

Haematoma, lead fracture and infection are the usual complications. However, careful and meticulous surgical technique can minimize the risk of these problems. Infection usually requires removal of the entire system. All procedures, therefore, must be undertaken using a sterile technique and with antibiotic prophylaxis. Another potentially serious complication is epidural haemorrhage, but it is rare (1:2000). A dural tap related CSF leak is usually self-limiting although it may be quite distressing to the patient and occasionally, it requires a dural patch. Patients on anticoagulation must be monitored extremely carefully for the risk of haematoma. In general, we stop aspirin ten days before the procedure.

Follow-up

Follow-up visits are conducted at 1 and 3 months following surgery and there after at 3 month intervals for a period of up to 2 years. At each visit, the patient undergoes clinical examination, exercise stress test, and an electrocardiogram. Data regarding episodes of angina, exercise duration, and ischaemia are reported after the IPG implantation. A decrease in the frequency of angina attacks and an increase in exercise duration have been demonstrated in these patients [26, 38].

Conclusion

SCS has become an important tool in the armamentarium of neurosurgeons and other specialists who are involved in the management of chronic pain problems. The current SCS systems are quite reliable and durable and the use of meticulous medical assessment and surgical technique minimizes the risk of infection. SCS has been demonstrated to diminish angina, reduce the frequency of hospital admissions, and improve the patient's quality of life [31, 40, 41]. These improvements appear to be long-term without carrying additional risks for the patients. SCS has been compared to the high-risk non-prognostic coronary artery bypass surgery in the ESBY randomised trial [34]. Both groups displayed significant reduction in the frequency of angina attacks and the requirements for short acting nitrates. However, the coronary surgery has a relatively much higher procedural mortality which compares to the negligible mortality of SCS. SCS seems to be effective in improving the quality of life in patients with intractable angina who are receiving maximal medical therapy and for whom no other acceptable surgical option exists. Indeed, activities of daily living and quality of life scores show consistent improvement in patients treated by SCS. One way to improve the manner in which the SCS impacts on the quality of life would be to employ the standardised instruments that are commonly used in assessments of the effects in other chronic pain patients. These instruments can be used prior to and at specified intervals after treatment; such evaluation procedures could provide objective data that would allow statistically valid comparisons.

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Diaphragm pacing with a spinal cord stimulator: current state and future directions

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Summary

Diaphragm pacing with electrical stimulation of the phrenic nerve is an established treatment for central hypoventilation syndrome. The device, however, is not readily available. We tested the same spinal cord stimulator we use for pain control in phrenic nerve stimulation.

We implanted a spinal cord stimulator (Itrel 3 or X-trel, Medtronic, MN) in 6 patients with chronic hypoventilation because of brainstem or high cervical cord dysfunction. The stimulation electrode was placed along the right phrenic nerve in the neck, and the device was implanted in the anterior chest. We used the cyclic mode, and set the parameters at 1 second ramp up, 2 seconds on, 3 seconds off. The pulse width and the frequency were set at 150 microseconds and 21 Hz, respectively. The amplitude of the output was adjusted to obtain sufficient tidal volume and to maintain $PaCO_2$ at around 40 mm Hg.

During a follow-up period up to four years, stable and sufficient ventilation was observed in all patients without any complications. Although further long follow-up is necessary, diaphragm pacing with the spinal cord stimulator is feasible and effective for the treatment of the central hypoventilation syndrome.

Keywords: Central hypoventilation; diaphragm pacing; spinal cord stimulator.

Introduction

Chronic hypoventilation caused by dysfunction of the brainstem or the high cervical spinal cord is a serious medicosocial problem. Patients in such hypoventilation state are usually managed with an artificial ventilator. However, chronic use of positive pressure ventilation is not physiological, predisposes to infections, and restricts the patient's activities. In addition, the cost of chronic respiratory care is substantial. It has been known for a long time that diaphragm pacing with an implanted electric device to stimulate the phrenic nerve is a reasonable solution for such patients [1, 3–5]. Almost all patients who have received diaphragm pacing so far have been implanted with a device specifically made for this purpose by Avery Laboratories Inc. (Commack, NY) [6, 7]. This device is not readily available in many countries including our own; we have applied, therefore, a spinal cord stimulatior (SCS) or deep brain stimulator for pain control in electrical stimulation of the phrenic nerves to pace the diaphragm. Our experience has shown the feasibility of diaphragm pacing with electrical stimulators which were originally created for pain relief [8, 10].

Stimulation parameters

Before applying the stimulator in the clinical setting, the waveform of the output from the stimulation device was checked. According to reports on optimal stimulation parameters for diaphragm pacing [6, 7], we tested various types of spinal cord or deep brain stimulators. We tried the Itrel 2 (Medtronic, model 7426), originally manufactured for deep brain stimulation for movement disorders, the Itrel 3 (Medtronic, model 7425) for pain control, the radiofrequency-driven X-trel system (Medtronic, model 3470) for pain control, and the Matrix dual output system (Medtronic, model 3272). We found that the Itrel 3 and the X-trel system had a cyclic output function suitable for artificial respiration. A dummy resistor of 1000 ohm was connected to the output and the waveforms were checked by an oscilloscope (Fig. 1). In this study, we set the parameters at the cyclic mode, 2 seconds on with 1 second ramp up, and 3 seconds off, resulting in the respiratory rate being 12 per minute. According to the stimulation parameters of the device specifically manufactured for phrenic pacing (Avery Laboratories Inc.) [6, 7], we set the pulse

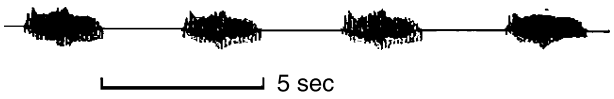

Fig. 1. Output of the spinal cord stimulator adjusted for phrenic pacing

width and the frequency at 150 microseconds and 21 Hz, respectively.

Indications

In order to achieve successful phrenic pacing, the function of the anterior horn neurons innervating the phrenic nerve should be intact. There should be no abnormality of the diaphragm itself. Therefore, cases of respiratory dysfunction due to intramedullary spinal tumors or amyotrophic lateral sclerosis were excluded. Cases of central hypoventilation due to high cervical injuries, brainstem vascular accidents, and idiopathic sleep apnea syndrome are the most appropriate for this treatment. The function of the peripheral phrenic nerve should be normal and this should be assessed with evoked diaphragm EMG, and percutaneous electrical stimulation of the phrenic nerve at the posterior border of the sternocleidomastoid muscle. However, the evoked diaphragm EMG may be false negative. The patient and the family members should be informed of the investigational character of the use of spinal cord stimulator for phrenic pacing. Details of the procedure and the importance of postoperative rehabilitation of the respiratory muscles are summarized in Table 1.

Operative technique

The patient is operated on under general anesthesia in the supine position with the head turned to the left side. Muscle relaxant is not used in order to allow us to monitor intraoperative contraction of the diaphragm, except at the induction of anesthesia. We usually implant the stimulation electrode to the right phrenic nerve, because the right lung has larger volume. A linear horizontal skin incision 4 cm in length is made, 4 cm rostral to the right clavicle, crossing the posterior border of the sternocleidomastoid muscle (Fig. 2). The subcutaneous tissue is dissected and the sternocleidomastoid muscle is retracted medially. After exposure of the anterior scalene muscle, the phrenic nerve is identified over the scalene muscle with monopolar electrical stimulation (5 or 50 Hz, 1 msec pulse width, 0.5–2 volts). Using an operative microscope, the nerve sheath is carefully exposed for about 1 cm in length; it is important that we do not dissect between the nerve and the scalene muscle in order to preserve vascular supply to the nerve. A quadripolar lead-type electrode for deep brain stimulation (Medtronic, model 3387-28) is placed along the nerve and fixed with two sutures to the surrounding connective tissues (Fig. 3). Another skin incision is made in the anterior upper chest, a subcutaneous pocket is created, the stimulation device is placed subcutaneously, and the lead is tunneled and connected to the lead electrode. First, we set the output of the stimulator in a mode similar to that in the studies in vitro. The amplitude of the output is adjusted so that tidal volume is approximately 500 ml. The most proximal contact of the quadripolar electrode to the stimulator is used as negative and the most distal contact as positive. Two contacts between them were set as ''off.'' After the operation, the carbon dioxide pressure of the exhalation and the arterial oxygen saturation in the fingertip are monitored until the values became stable. The carbon dioxide pressure in the end tidal air is adjusted to about 40 mm Hg by changing the output voltage of the stimulator. To avoid fatigue of the phrenic nerve and diaphragm [1, 5, 6], we use the stimulator only in the daytime in patients who required artificial ventilation for 24 hours. For patients with sleep apnea but sufficient ventilation in the awake state, we train the patient to switch on the device before going to bed.

Table 1. *List of patients*

Patient no.	Age (yr)	Cause of hypoventilation	Condition	Hypoventilation duration (mo)
1	58	SAH due to vertebral artery aneurysm, intraoperative rupture	sleep apnea, respirator ''on'' only at night	6
2	58	operative complication of jugular foramen neurinoma	totally dependent on respirator	4
3	63	spontaneous brainstem hemorrhage, no operation	totally dependent on respirator	8
4	55	spontaneous brainstem hemorrhage, no operation	totally dependent on respirator	3
5	34	AAD surgery complication	totally dependent bilateral implant	9
6	42	gun shot/C1-2 cord injury	totally dependent	14

mo Months, *SAH* subarachnoid hemorrhage, *AAD* atlanto-axial dislocation.

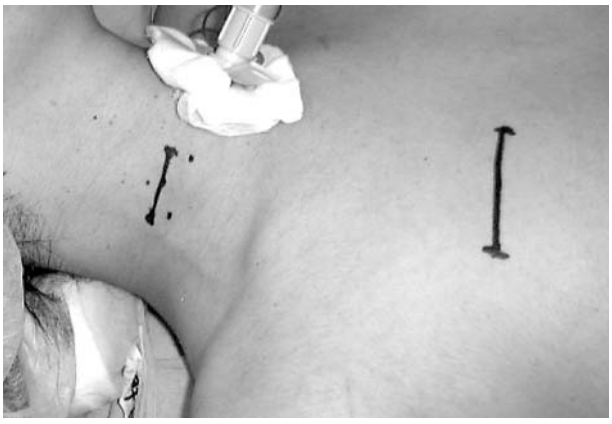

Fig. 2. Skin incision

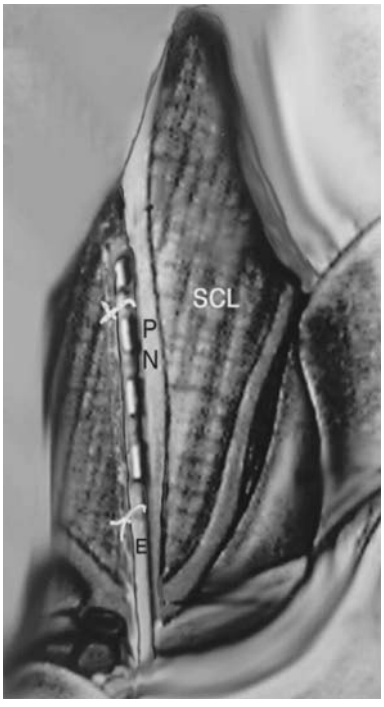

Fig. 3. Stimulation electrode placed in a position adjacent to the phrenic nerve

Postoperative management

The long-term positive pressure ventilation results to the respiratory muscles becoming usually atrophic and in some patients, even with phrenic pacing, sufficient tidal volume may not be established. Fatigue of the diaphragm after short period of phrenic pacing is also common. Therefore, gradual and stepwise diaphragm muscle training is very important. In the beginning, five minute pacing and 15 minute rest is repeated for several hours. Pacing time is gradually increased over the next several weeks or months.

Discussion

Artificial ventilation with phrenic nerve stimulation has a long history [5, 6]. After an appropriate device became commercially available by Avery Laboratories Inc, it has been implanted in many patients [1, 3, 4]. The efficacy and problems related to the device in this treatment have been documented in detail [1–5]. The reason we started using the spinal cord stimulator for diaphragm pacing is that the stimulator made specifically for phrenic nerve stimulation is not readily available in our country. The Ministry of Health and Welfare in Japan has not approved the Avery Laboratories stimulator for medical use. As a result, the cost of this device is not reimbursed by medical insurance in Japan. We think that similar problems may exist in many other countries. We have to solve such domestic problems properly, but in the meantime, our patients cannot wait. In contrast to the lack of availability of the Avery device for diaphragm pacing, the spinal cord stimulator is commonly used and covered by insurance in Japan, when it is used for pain control. Thus, these are no big hurdles in the use of spinal cord stimulators. The longevity of the battery in the Itrel 3 stimulator is about 5 years when used for pain control with continuous output. The usual stimulation parameters for pain control are 50 Hz, 200 microsec pulse width, 3 volts, and 8 hours continuous use per day. The comparison of these parameters with the output parameters for diaphragm pacing, in the present cases, revealed that in diaphragm pacing the consumption of electricity was only about 12.5% of the consumption in pain management. Simple calculation of these data indicates that the battery longevity of the Itrel 3, when used for phrenic nerve stimulation, is 8 times longer than in spinal cord stimulation for pain control. We also used an electrode for deep brain stimulation (DBS) and placed it along the phrenic nerve. Ideally, the stimulation electrode should be atraumatic to the nerve and with features that would allow it to be securely fixed, like the spiral shaped electrode for vagal nerve stimulation for intractable epilepsy. With DBS or SCS electrodes, it is known that the electrical current could spread to the surrounding tissues. We were worried, therefore, that local muscle contraction or electrically evoked sensation could cause problems to the patients. However, we did not experience any such problems.

Recently, new approaches have attempted to restore respiratory function by simultaneous stimulation of both diaphragm and intercostal muscles and laparoscopic direct stimulation of motor points in the diaphragm [2, 9].

Although these new approaches are promising, currently they are not widely available.

The use of a spinal stimulator for diaphragm pacing has no warranty from the manufacturer, i.e. this is an ''off-label'' indication. An emergency backup system has not been established. Therefore, we have performed the procedure solely on our own responsibility. Although long-term follow-up is necessary, we conclude that the spinal cord stimulator system can be used for phrenic nerve stimulation for diaphragm pacing as an alternative neuromodulatory treatment.

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Neuroprostheses for management of dysphagia resulting from cerebrovascular disorders

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Summary

Swallowing is a complicated process that involves intricate timing between many different muscles in the mouth and neck. The primary purpose of swallowing is to move food through the mouth and pharynx and into the esophagus for transport to the stomach for digestion. Dysphagia is a general term that refers to a disruption in any part of the process. The consequences of dysphagia include social embarrassment; malnutrition; and aspiration. Of these, aspiration is the most significant as it is associated with a significantly greater risk of pneumonia and death. If patients fail to adequately protect the airways with standard exercise and therapy, they are often disallowed from taking food by mouth and receive nutrition by alternate means. If patients still experience frequent pneumonia, more drastic surgical measures that permanently separate the airway from foodway are required. As an alternative to these surgical procedures, neuroprostheses can dynamically restore airway protection. There are two primary protective mechanisms that neuroprostheses seek to restore. The first is laryngeal elevation and the second is vocal fold closure. The present article is an introductory overview of the swallowing process, the primary muscles and nerves related to swallowing, the effects of dysphagia, the standard treatment options, and the neuroprosthetic options.

Keywords: Dysphagia; swallowing disorders; larynx; vocal folds; electric stimulation; cerebrovascular accident; rehabilitation; cerebrovascular disorders.

Introduction

Dysphagia is a broad term that generally refers to any ''difficulty in swallowing.'' Swallowing is a complicated process involving an intricate coordination of both voluntary and involuntary actions through multiple stages of bolus preparation and transport to the stomach. Disruption to sensory, muscular, or control aspects of any of these stages results in various swallowing deficits ranging from leakage of food from the mouth to entry of foreign matter into the lungs. The consequences of these swallowing deficits range from social embarrassment to pneumonia and death. Traditional treatments for dysphagia range from therapy, strengthening exercises, and altered positions during swallowing to restricted diet to radical surgery of the larynx, esophagus, and vocal folds. While many patients respond well to basic, non-surgical solutions, thousands of patients per year require surgical approaches to adequately keep foreign matter from entering the lungs. In this chapter, we discuss the use of neuroprostheses and electrical stimulation as an alternative to radical surgical approaches for management of the most advanced dysphagia in patients. Neuroprostheses for the head-and-neck is a rapidly emerging and promising new field.

Overview of swallowing

Swallowing is the act of forming food into a bolus and then transporting it to the stomach for digestion. The entire process is characterized by three phases: oral, pharyngeal, and esophageal. The associated primary musculature (Fig. 1) and innervation of each phase are briefly described in the following sections. This is not meant to be an exhaustive description of the swallowing process, but emphasizes key structures and functions that are particularly important to various forms of dysphagia and are potential targets for functional electrical stimulation (FES) or neuromodulatory intervention (Table 1).

Oral phase

The oral phase is initiated when food is introduced to the oral cavity. The lips, and specifically the orbicularis oris, buccinators, and zygomatic muscles, which are

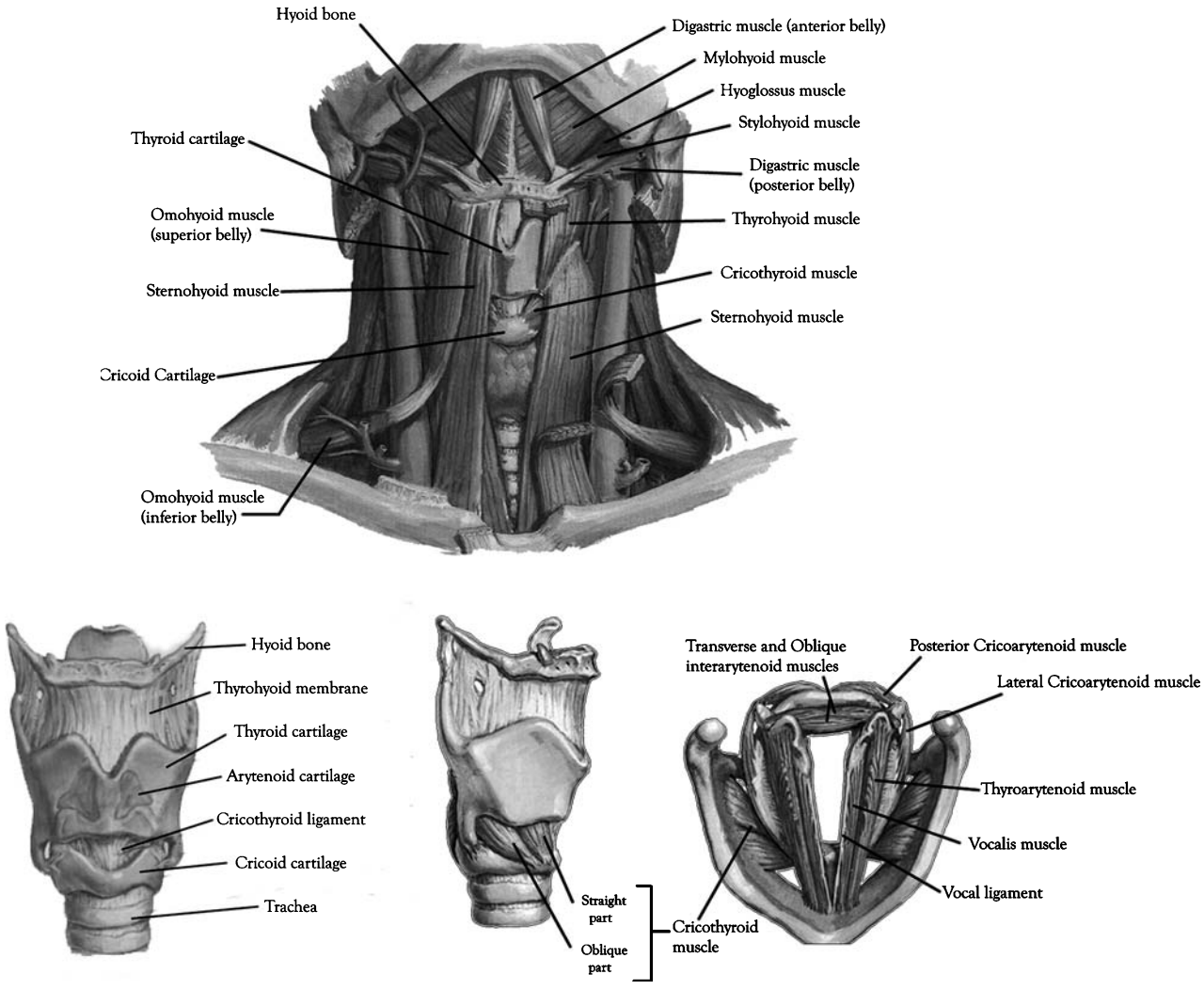

Fig. 1. Overview of relevant muscular and structural anatomy related to swallowing. The top panel shows the extrinsic muscles of the larynx, which are predominately responsible for motion of the larynx. The bottom panels show the structural components of the larynx and the intrinsic muscles, which are predominately responsible for closure of the vocal folds. The figures are modified from [73]

innervated by the facial nerve (VIIth cranial nerve), maintain closure of the oral cavity, keep the bolus in the mouth, and keep the food in the teeth during chewing. The multiple muscles of the tongue include the genioglossus, hyoglossus, styloglossus, and the intrinsic muscles of the tongue. These are all innervated by the hypoglossal nerve (XIIth cranial nerve). With solid or semi-solid foods that require chewing, the tongue and lips work the bolus into and out of the teeth. When the food is properly masticated into a pasty consistency or when puree and liquid consistencies are presented, the tongue works the food into a well-formed bolus and moves it to the back of the oral cavity. In the final stage of the oral phase, the tongue, starting from the tip and moving back to the center of the tongue seals against the hard palate. The bolus is moved to the back of the mouth. The posterior part of the tongue then propels the bolus into the pharyx. The seal of the tongue is critical to generation of pressure within the pharynx, which is required to move the bolus through the pharynx and into the esophagus. The entire oral phase is under voluntary control from higher cortical regions of the brain.

Pharyngeal phase

The pharyngeal phase begins when the food is thrust into the oropharynx. The bolus triggers several sensory organs in the anterior pillars of the fauces, in the posterior pharynx, and on the epiglottis [75]. The IX (glossopharyngeal) and X (vagus) nerves heavily innervate these areas [72]. Particularly, the pillars are innervated by a plexus of IX and X. The epiglottis,

Table 1. *The primary muscles of swallowing and airway protection*

Phase	Innervation	Muscle/sensory organ	Action
Oral	facial (VII)	buccinator orbicularis oris zygomaticus	chew the food and form into a bolus
	mandibular nerve (V_3)	masseter	
	hypoglossal (XII)	intrinsic muscle of the tongue	form the bolus and move into the hypopharynx
	glossopharyngeal (IX)	pillars of fauces	initiate swallow reflex
	superior laryngeal nerve (X)	epiglottis sensors	
Pharyngeal	mandibular nerve (V_3)	mylohyoid	raise and move the larynx anteriorly
	facial (VII)	stylohyoid	
	hypoglossal (XII)	geniohyoid thyrohyoid	
	superior laryngeal nerve (X)	cricothyroid	adduct the vocal folds
	recurrent laryngeal nerve (X)	thyroarytenoid interarytenoid lateral cricoarytenoid upper esophageal sphincter	

postcricoid, and arytenoid are densely innervated by the internal branch of the superior laygneal nerve (iSLN), which is a branch of the X nerve. These send a volley of activity to the nucleus of the solitary tract and dorsal swallow group in the medulla. Stimulation of these nerves in animals has been shown to reliably and repeatedly produce a swallow [4, 46, 53, 78]. Stimulation of the iSLN in humans modulates the swallowing reflex, but initiation of an entire swallow sequence was not reported [7].

A complex pattern generator in the brainstem predominately located in the Nucleus Tractus Solitarius (NTS), ventral swallow group, and the nucleous ambiguous takes over the swallow. From this point forward, the swallow is involuntary. Neurons from the ventral swallow group project to the motor nuclei of the Vth, VIIth, Xth, and XIIth cranial nerves and the C1 to C3 spinal cord levels. As well, there is interaction between the swallow pattern generators and the respiratory pattern generators [46] such that respiration is inhibited during the swallow event.

The four most important actions of the pharyngeal phase are the pistoning of the tongue, elevation of the larynx, closure of the vocal folds, and relaxation of the cricopharyngeus muscle or upper esophageal sphincter. The pistoning of the tongue primarily serves two purposes. First, the epiglottis is attached to the base of the tongue and as the tongue pushes posteriorly, it passively flips the epiglottis over the tracheal inlet. Second, the tongue propels the food through the pharynx into the esophagus.

The motion of the larynx during a swallow is extensive. This is easily palpated by placing a finger on the throat during a swallow. On average, it has been shown that the larynx moves approximately 12 mm both upward and 12 mm forward [8, 60]. This elevation of the larynx aids in flipping the epiglottis over the tracheal inlet. More importantly, however, it pulls the inlet up and forward, under the base of the tongue. Moving the larynx up under the tongue effectively takes the airway out of the food's path of travel to the esophagus. Further, the motion of the larynx aids in the opening of the esophageal inlet as the cricopharyngeus muscle relaxes.

The motion of the larynx is controlled by the extrinsic, suprahyoid muscles of the larynx. These muscles and their innervations include the mylohyoid and anterior digastric muscles which are innervated by the mylohyoid branch of the mandibular branch of the trigeminal nerve, V_3; the stylohyoid and posterior digastric muscles innervated by the facial nerve, VII; the stylopharyngeous muscle innervated by the glossopharyngeal nerve, IX; and the geniohyoid and thyrohyoid muscles innervated by the hypoglossal nerve, XII. Of these, the mylohyoid, geniohyoid, and thyrohyoid muscles are the most important [41].

The third important element of the pharyngeal phase is the closure of the false and true vocal folds. The closure pressure between the vocal folds during a swallow has been measured at 250–300 mmHg. With maximum strained voluntary closure, the pressure only gets to about 320 mmHg and during coughing the closure pressure is slightly less than during swallow [79]. This closure creates a valve or barrier on the top of the trachea to further prevent entry of food into the airway.

The motion of the vocal folds is controlled by the intrinsic laryngeal muscles. These are a set of five bilateral muscles comprised of the cricothyroid, thyroarytenoid, interarytenoid, lateral cricoarytenoid, and posterior cricoarytenoid muscles. Of these muscles, all but the posterior cricoarytenoid act to close the vocal folds and the laryngeal inlet. The posterior cricoarytenoid muscle opens the vocal folds and airway. All of the intrinsic laryngeal muscles are innervated by the recurrent laryngeal nerve (RLN), which is a branch of the vagus nerve, X. The cricothyroid also receives innervation

from the external branch of the superior laryngeal nerve (eSLN), which is also a branch of the vagus nerve [77].

Esophageal phase

The esophageal phase begins after the food has traveled through the pharynx and when it enters the esophagus. At this point, the peristaltic action of the muscles of the esophagus carries the food to the stomach. Once the food is safely in the esophagus, the risk of aspiration and other significant complications of dysphasgia are significantly reduced. There is a complicated pattern generator in the solitary nucleus, the nucleus ambiguous, and dorsal motor nucleus of the vagus nerve that mediates the peristalsis of the esophageal smooth muscles [52]. Both the vagus nerve and sympathetic nervous system carry signals controlling the esophageal phase of swallowing.

During this phase, the components of the oral and pharyngeal phases are reset. The vocal folds are opened, the larynx is returned to its resting position, the tongue is returned to its resting position, the epiglottis flips up, and the swallowing mechanism is reset for the next presentation of food.

Dysphagia and its consequences

Dysphagia is a generic term that refers to any swallowing difficulty or disorder. Therefore, the types of dysphagia and the consequences of dysphagia are quite different in different phases of swallowing. An introduction to the most common types of dysphagia in each phase and to some of the consequences of each is provided in this section. Aspiration, which is the most dangerous consequence of dysphagia is discussed often in the following sections, and is defined as the entry of food or foreign matter into the upper airway, past the true vocal folds.

Oral phase

Since the oral phase of swallow is under voluntary control by the cortical swallow region, dysphagia in this phase typically results from a cortical stroke, damage to the VIIth motor nucleus, and damage to the XIIth motor nucleus. One common form of dysphasgia in this phase is poor labial control. For example, a patient with hemiparesis and facial droop often cannot form a complete seal with the lips. Consequently, during bolus formation and mastication, it is difficult to maintain control of the bolus and contain it within the mouth. This results in drooling and leakage of food. An obvious complication of this form of dysphagia is the social consequences. More importantly, excessive leakage can result in the inability to intake adequate nutrition resulting in malnutrition.

The lack of tongue coordination and control results in poor bolus formation, poor or delayed transit, inadequate pressure generation, and premature leakage of food into the pharynx. Inadequate pressure generation often makes it difficult for the food to enter the esophagus. This results in residue in the pharynx following the swallow, and often aspiration of the residue. Premature leakage of the food into the pharyngeal vestibule often results in pooling of material above the vocal folds and trachea, where the leaked food can be aspirated prior to initiation of the pharyngeal phase of swallow.

Finally, at the end of the oral phase, inadequate tongue control, lack of sensory feedback, or incomplete voluntary control can result in difficulty initiating the involuntary pharyngeal phase of swallow. Patients will often require several attempts to initiate a swallow. This can result in fatigue and inadequate nutrition. If the food is moved into the pharynx without initiation of the pharyngeal swallowing mechanisms, food can pool in the larynx with subsequent aspiration.

Pharyngeal phase

The pharyngeal phase is involuntary, controlled by a pattern generator and motor nuclei in the medulla. A brainstrem stroke, particularly of the middle cerebral artery and anterior lesions of the periventricular subcortical white matter [44, 57–59], often results in pharyngeal-phase dysphagia with intact motor neurons. The various forms of dysphagia in the pharyngeal phase include poor or absent laryngeal elevation, inadequate or uncoordinated vocal fold closure, esophageal constricture, valecullar residue, and inappropriate clearance.

Absent laryngeal elevation and inadequate or uncoordinated vocal fold closure leave the upper airway open or compromised during the swallowing effort. As the tongue propels the food into the pharynx, without protection, some of the food is aspirated. This is exacerbated with increasing bolus size and especially if the esophageal inlet is constricted. When the upper esophageal sphincter is closed, increased pressure produced by the tongue drives the bolus into the airway.

The pharyngeal phase and its associated forms of dysphagia are particularly dangerous. These are most likely to result in entry of food and infectious material into the airway. Aspirating patients are at a much higher risk of

developing pneumonia and other health complications. Therefore, most of the present FES applications for management of dysphagia focus on the pharyngeal phase.

Esophageal phase

Difficulties in the esophageal phase include inadequate peristalsis and inadequate opening of the lower esophageal sphincter. The typically result is poor or incomplete transport, resulting in difficulty in getting adequate nutrition.

Summary

Dysphagia is a generic term that encompasses many different aspects of swallowing deficiencies. In the preceding section, the various types of dysphagia were presented as occurring in isolation of each other. Typically, patients exhibit multiple aspects of dysphagia.

The consequences of dysphagia range from social embarrassment to inadequate nutrition to aspiration. Inadequate nutrition can be augmented by alternate means of alimentation. Current efforts at electrical stimulation for dysphagia management focus on the prevention of aspiration as it tends to have the most significant consequences. When foreign matter enters the lungs, it often carries infectious agents. Aspirating patients have a 20-fold increase in chances for developing pneumonia [61, 81], which is a leading cause of mortality, especially following stroke.

Aspiration can be either silent or patent. The upper airway is normally very sensitive to foreign matter and the entry of foreign matter causes a violent coughing reaction. This is referred to as patent aspiration. Everybody tends to aspirate from time-to-time, but typically manage the aspiration with reflexive coughing. In patients with diminished or absent sensation, the coughing reaction is absent. This is referred to as silent aspiration. Since the patient does not cough, the foreign matter is not expelled. Worse, it can be difficult to diagnose without proper videofluorographic tests.

Incidence/prevalence

Dysphagia is not a primary condition, but usually a complication or symptom of another condition. The causes of dysphagia can be categorized as neurologic, infectious, oncological, systemic, anatomical abnormalities, pharmacologic, or idiopathic [69]. Diseases of the motor system, such as amyotrophic lateral sclerosis (ALS), myasthenia gravis, Guillain-Barré syndrome, postpoliomyelitis syndrome, and iatrogenic damage to the recurrent laryngeal nerve (RLN) are not generally candidates for FES systems as these typically require an intact motor nerve. There are exceptions, of course, and successful examples of stimulation of dennervated muscle [9, 63, 76, 83–85].

Stroke and other central nervous system conditions, such as traumatic brain injury, cerebral palsy, Parkinson's, and multiple sclerosis, are good candidates for FES interventions with intact motor neurons. In this chapter, the discussion focuses specifically on stroke, but the conclusions are applicable to many central vascular disorders or traumatic injuries. There are many variants of a stroke, disease, and trauma that depend on the type, location, and extent of the accident.

Aspirated materials often contain infection materials that lead to pneumonia. Since swallowing is a complicated process that is controlled by many areas of the brain, damage to any area of the brain often results in some form of dysphagia. Cerebrovascular accidents of the middle cerebral artery, for example, are associated with significant evidence of dysphagia. Of the between 590,000 (National Stroke Association) and 730,000 [10] stroke survivors each year in America, dysphagia occurs in 74% of the patients, or as many 570,000 patients each year! Dysphagia is so common that a speech-and-language pathologist is considered an important member of the stroke response team and swallowing evaluation is part of the standard test battery administered following a stroke [43]. Many patients will recover swallowing function following stroke as a result of neural plasticity and therapy. However, chronic aspiration will occur in 19% to 38%, or about 150,000 patients per year in the U.S. [5, 45, 68, 81].

The dysphagia-related co-morbidity in stroke is significant. Malnutrition occurs in approximately 36% of all stroke patients and 48% of the dysphagic patients. Approximately 12% of aspirating patients will develop pneumonia, a 20-fold increase over non-aspirating patients [61, 81]. Aspiration pneumonia is responsible for 20% of stroke-related deaths in the first year after the onset of the stroke and 10–15% of the deaths in the following years. This equates to between 11,000 [1] and 40,000 [5] aspiration-related deaths every year in the United States alone. Similar trends were observed in a study in the U.K. [64].

Dysphagia treatment pathways

The standard pathway for aspiration treatment (Fig. 2) is progressively more aggressive. Each progressive step

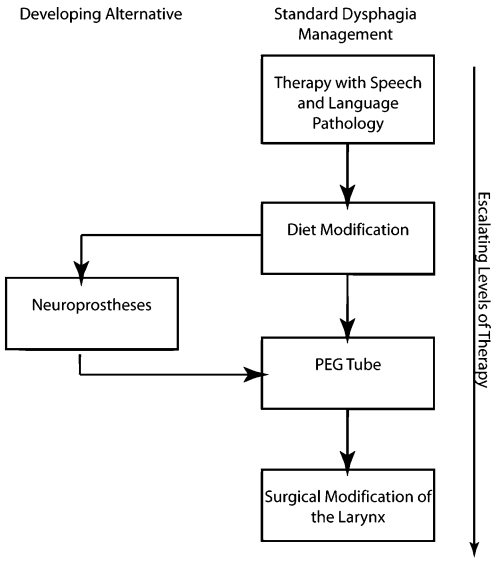

Fig. 2. Dysphagia treatment pathways. The standard pathway proceeds from non-invasive, minimally destructive therapy, exercise, and rehabilitation to diet modification to no oral intake with alternative alimentation to surgical modification of the pharynx and larynx. Functional electrical stimulation provides an alternative that is between diet modification and no oral intake

in therapy has significantly greater effect on the patient quality of life. Swallow therapy and diet modification with a speech therapist and dietician are the most conservative interventions and the standard intervention in the acute phase of stroke. Therapy consists of strengthening exercises, compensatory positioning and maneuvers, and mechanical and thermal stimulation [43]. The compensatory positioning includes tucking the chin to the chest, tilting the head to a side, and patient positioning. The exact positioning chosen depends on weaknesses observed during swallowing evaluation. In all these techniques, the primary objective is to affect the pathway of food through the pharynx and divert it from the airway. Maneuvers include forceful swallow where the patient contracts the chest and abdomen, similar to a cough. This helps to close the vocal folds and generate pressure in the pharynx to direct food to the esophagus. Another technique is to physically hold the larynx in suspension with the hand during the swallow. This aids in laryngeal suspension and keeping the airway out of the food pathway. Thermal stimulation techniques, such as a cold mirror in the back of the mouth, seek to aid in initiation of the swallowing reflex by stimulation of the sensory pathways normally responsible for swallow initiation.

Patients that are unable to recover sufficient swallowing capabilities with these therapies often need alternate means of nutrition, such as percutaneous endoscopic gastrostomy (PEG) tubes. These tubes, however, require attention and are associated with increased morbidity [5]. A tracheostomy is often required to secure airway access and avoid flooding of the lungs by normal secretions (e.g. saliva) and ingested materials [6]. Even with PEG feeding tubes, patients typically desire taking food by mouth and do not always comply with strict orders for no oral intake. Even the most compliant patients will have significant salivary and other secretions that are typically swallowed in a day. Therefore, some form of long-term surgical separation of the airway and foodway often becomes necessary to avoid pneumonia and its complications. These are mutilating surgeries, such as total laryngectomy, supraglottic closure, glottic closure, partial cricoidotomy, double barrel tracheostomy, modified epiglottalplasty, and laryngeal suspension. These procedures often involve irremediable voice compromise [16], cost, and co-morbidity.

Unfortunately, all of the surgical solutions involve permanent manipulation and often destruction of the larynx or other structures. Neuroprostheses offer an alternative, dynamic approach that can re-animate, coordinate, and drive the muscles of the larynx to restore swallowing function and most importantly protection of the airway. Functional neuromuscular stimulation is an attractive solution that is positioned between non-invasive treatments and mutilating surgery (Fig. 2).

Neuroprostheses for dysphagia

Early feasibility demonstrations

The most important goal of current neuroprosthesis development for the management of dysphagia is protection of the airway. The first use of electrical stimulation to treat laryngeal dysfunction in the human was reported by Broniatowski et al. [18] for stimulation of a reinnervated posterior cricothyroid muscle for vocal fold opening. Since, Broniatowski and colleagues have exhaustively examined several animal models of laryngeal and esophageal pacing [11–15, 17, 19–40, 55, 56, 62].

Friedman *et al.* [49] reported laryngeal stimulation to treat laryngeal dysfunction in the humans. They used percutaneous electrical stimulation of the RLN in patients with spastic dysphonia for temporary treatment and screening of patients for an implanted system. Using a flexible endoscope, they observed that varying the stimulator frequency could control the vocal cord position.

In a subsequent study, five patients were implanted with permanent systems. These first systems used either an elongated oval plate implanted near the RLN or a nerve cuff electrode. Their pulse generator was implanted on the chest wall. Stimulation current ranged from 0.5 to 3.0 mA and frequency from 20 to 30 Hz. Pulse width was 160 μsec. At one month after implantation, recordings of four patients demonstrated significant improvement in vocal quality during stimulation compared with baseline values without stimulation. One patient developed vocal cord paresis, a significant complication of the procedure.

Their initial study group was limited primarily due to concern about the safety of implanting a nerve stimulator around the vagus nerve, which has a very broad distribution extending to the heart and viscera. The RLN is a branch of the vagus nerve. Other subsequent studies with electrodes implanted directly on the vagus nerve showed absence of changes in vital signs and electrocardiograms, thus establishing the systemic safety of vagal nerve stimulation [48] and RLN stimulation.

Building from this early work, several groups are aggressively investigating various mechanisms to manage dysphagia and aspiration specifically. The primary focus is on the pharyngeal phase of the swallow. As discussed previously, there are three primary components in airway protection in the pharyngeal phase: epiglottis flip, laryngeal elevation, and vocal fold adduction. The epiglottis contains some musculature, but is predominantly a passive tissue flap that is flipped down over the airway in response to the posterior thrust of the tongue and the elevation of the larynx. Laryngeal position is controlled by the extrinsic musculature of the larynx. Elevation is predominately produced by superior extrinsic muscles, namely the mylohyoid, thyrohyoid, and geniohyoid muscles. Vocal fold position and tension is controlled by the intrinsic muscles of the larynx. The closure of the vocal folds is caused by 4 of the 5 bilateral pairs of muscles, namely the thyroarytenoid (TA), lateral cricoarytenoid (LCA), cricothyroid (CT), and interarytenoid (IA) muscles.

Targeting a mechanism for management of aspiration

The relative contribution of each of these three mechanisms to protection of the airway in the human is not well-known. Investigations in the cat, however, have shown that transection of the elevation muscles results in aspiration in 20% of the subsequent swallows. An added epiglottectomy did not significant change the percentage of aspiration. However, added cordectomy result in aspiration in nearly 100% of the subsequent swallows. Unilateral cordectomy did not result in aspiration compared to the normal animal. Bilateral cordectomy with all the laryngeal elevation musculature and epiglottis still intact resulted in aspiration of 100% of the subsequent swallows [71].

Studies in humans using percutaneous stimulation have shown a potentially stronger role for laryngeal elevation in the human than indicated from the studies in felines. During a typical swallow, the hyoid and consequently, the airway is moved superiorly and anteriorly approximately 12 mm in each direction [60]. This serves three important functions. First, it moves the trachea opening up and under the tongue and out of the pathway of the food. Second, it helps to passively flip the epiglottis over the airway. Third, it tends to passively pull on the esophageal inlet, helping to open the foodway as the cricorpharygeous muscle relaxes to allow food passage. It should be noted, however, that it has been shown that stimulation of the RLN and activation of the intrinsic laryngeal muscles also acts to open the upper esophageal sphincter [50, 51].

Given the conflicting and equally compelling data about relative importance of the mechanisms of protection, there are two primary neuroprosthetic approaches developed for management of aspiration. One stimulates the extrinsic muscles to elevate the larynx during swallowing and the other stimulates the intrinsic muscles to close the airway during the swallow. Each of these approaches has inherent advantages. The design considerations and stimulation studies related to each approach are discussed next.

Neuroprostheses for laryngeal elevation

One significant advantage of neuroprostheses to produce laryngeal elevation is that the muscles, especially the geniohyoid muscle, bilateral mylohyoid muscles, and bilateral thyrohyoid muscles, are superficial. Consequently, these muscles are easily amenable to minimally invasive muscle stimulation technology, such as surface and intramuscular electrodes. This accessibility has been exploited to study the effects of laryngeal elevation directly in human subjects. It is also worth noting that these muscles are innervated by different nerve supplies. The mylohyoid muscle is innervated by the mandibular branch of the trigeminal nerve (V_3) and the geniohyoid and thyrohyoid muscles by hypoglossal nerve (XII). In addition to their accessibility, these muscles are relatively large and can easily accommodate muscle-based

electrodes. Nerve-based or cuff approaches can be more problematic. The XII nerve is easily accessible, but accessing the V_3 is difficult. Therefore, muscle-based stimulation approaches opposed to nerve-base stimulation approaches are a logical design choice.

Electrical stimulation of these muscles has been shown to reproduce a significant portion of laryngeal elevation [8, 41]. Stimulation of single muscles produced approximately 30% of the normal laryngeal elevation. Stimulation with pairs of muscles produced approximately 50% of the normal laryngeal elevation.

The least invasive approach is to use surface electrodes. With two electrodes placed over the submandibular glands, it is possible to stimulate the mylohyoid and digastric muscles and with high enough stimulus may even stimulate the geniohyoid muscle. By adding a third reference electrode attached to the earlobe or other remote location, the surface electrode can also record the activity of the ''submental complex'' or general activity of the tongue. This activity is correlated with swallow initiation [8, 47, 70, 74]. Using the submental activity as a trigger for stimulation, the effects of stimulation with the submandibular electrodes has been examined using videofluoroscopy. Stimulation was shown to increase the size of the esophageal inlet and reduce bolus penetration into the laryngeal vestibule during swallowing [65]. To date, the efficacy of electrical stimulation that produces laryngeal elevation to reduce aspiration has not been demonstrated in the human.

Neuroprostheses for vocal fold closure

The intrinsic muscles of the larynx control vocal fold closure. These muscles are small and deep within the neck and laryngeal cartilages. Accessing them with surface stimulation is very difficult or not possible. Percutaneous intramuscular electrodes [66, 67], however, have been placed into the thyroartenoid (TA) muscles. Electrical stimulation of these muscles has shown a reduction in the opening in the glottal chink and restriction of the space of the upper airway [66]. Chronic stimulation of the TA with intramuscular electrodes has been shown to maintain a dynamic control of vocal fold closure [67].

Another approach is stimulation of the recurrent laryngeal nerve with nerve cuff electrodes. Animal trials have shown that stimulation of the RLN will produce a net closure of the vocal folds [14, 17, 20, 24, 25, 37, 38]. Of the five bilateral pairs of intrinsic muscles, only the posterior cricoarytenoid (PCA) opens the cords. When all of the muscles are stimulated with whole nerve stimulation of the RLN, the closing muscles override the opening and produce vocal fold closure. Therefore, selective stimulation of the laryngeal intrinsic muscles is not necessary and stimulation of the RLN with a simple, whole-nerve cuff electrode is an attractive approach.

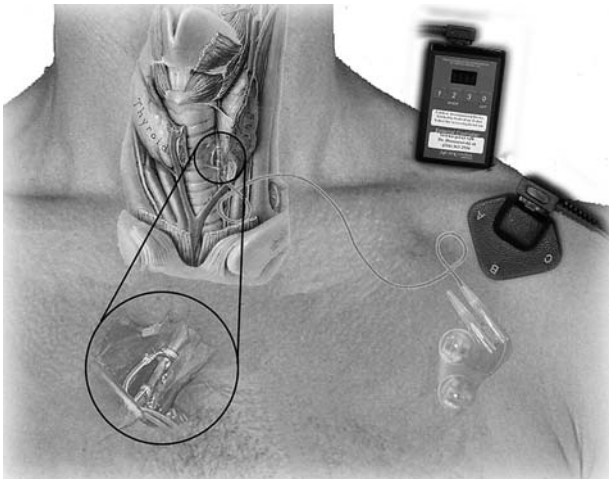

Fig. 3. System for stimulation of the recurrent laryngeal nerve for vocal fold closure. A bipolar helical electrode [2, 3] is placed on the recurrent laryngeal nerve. A single channel Finetech Medical (www.finetech-medical.co.uk) stimulator is implanted in a subcutaneous tissue pocket approximately 2 cm inferior to the clavicle. The lead from the electrode is tunneled subcutaneously and connected to the stimulator. Power and stimulation timing is transferred to the stimulator by a transcutaneous inductively linked signal. The subject or caregiver initiates stimulation by pressing a button on the external controller, which initiates a preprogrammed stimulation pattern

This approach has been implemented in a small human feasibility trial. The system is composed of a modified Finetech single channel stimulator and a Huntington Medical Research Institute (HMRI) bipolar helical electrode (Fig. 3). The HMRI electrode has been implanted in over ten-thousand patients for the control of epilepsy [54, 80, 82]. For the aspiration study, subjects were recruited from patients that were at least one year post-injury, had failed standard therapy treatments, were chronically aspirating, and were candidates for tracheostomy tubes. These patients had exhibited chronic aspiration that required them to not take anything by mouth and they received their nutrition through PEG-tubes.

In the only reported case study to date, stimulation of the RLN nerve has shown strong vocal cord closure and a reduction in aspiration [40]. Using a flexible fiberoptic endoscope, complete vocal fold closure correlated with electrical stimulation was directly visualized. The study implemented unilateral, not bilateral, RLN stimulation and demonstrates that this is sufficient to cause the vocal fold to cross midline and close against the contralateral cord. To examine the effect of RLN stimulation on

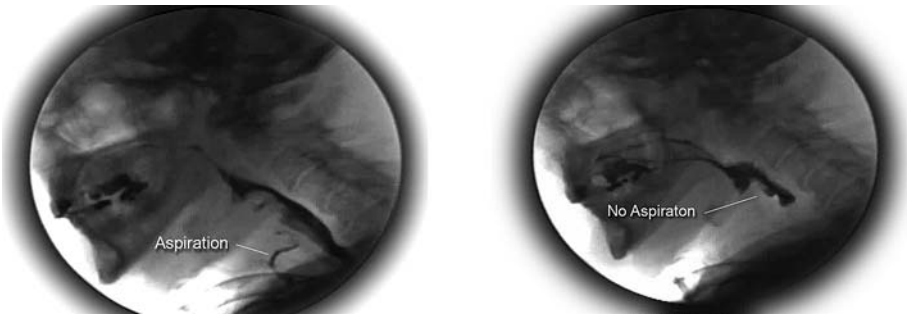

Fig. 4. Frame captures from modified barium exams comparing no stimulation to stimulation. The left panel shows significant aspiration of thin liquid during the swallow when stimulation is not active. The right panel is the next swallow of thin liquid with the stimulation active and the aspiration is arrested

aspiration, modified barium swallow examinations were administered with and without stimulation (Fig. 4). These demonstrated a statistically significant (t-test of proportions, $\alpha < 0.05$) reduction in incidence of aspiration with stimulation compared to without stimulation.

In this early system, the stimulation was controlled by an external stimulator. Stimulation is activated when the subject or a caregiver pressed a button on the external controller. The subjects were instructed to start stimulation when food is entered into the mouth and leave it on until after two swallows. Two swallows is a standard technique taught to reduce the pharyngeal and vallecular residuals. In this early stage of development, the long stimulation time is important to protect against aspiration of premature leakage during the oral phase and aspiration of residues in the pharyngeal space. The modified barium swallow tests, which directly visualize the bolus of food as it travels through the swallow, showed that most of the protective benefits occurred pre- and post-swallow.

The concern is that prolonged closure of the vocal folds would prevent respiration. In the case of the feasibility trial, however, this was not a problem as the subjects had a tracheostomy tube to provide a patent airway. This does present a challenge that will need to be addressed before a system can reasonably be a clinical standard of care. Another challenge is to eliminate the external button control of the device or integrate it into the patients' daily feeding routines. It has been shown that healthy volunteers can self-trigger stimulation to coordinate with reflexive swallowing [42]. It remains to be shown that a stroke patient can coordinate self-triggering with swallowing. Unfortunately, any system relying on patient or caregiver input may work for meals, but is not likely to provide protection from the normal swallowing of saliva and other secretions throughout the day.

In summary, electrical stimulation has been shown to produce elevation of the larynx and has been shown to produce closure of the vocal folds. Elevation is best achieved using muscle-based electrodes and stimulation approaches while vocal fold closure is best achieved with RLN stimulation and nerve-base approaches. The efficacy of these different methods on the reduction of aspiration is yet to be proven. To date, there has not been a report of a completed, randomized, blinded clinical trial to demonstrate the clinical efficacy of any of the devices to reduce or prevent aspiration or ultimately to reduce the incidence of aspiration-related pneumonia. Pilot clinical trials to show the clinical feasibility of both of these systems are underway, but there are still significant technical barriers and challenges to be overcome. Despite years of research and a fairly complete understanding of the critical elements of swallowing, the use of electrical stimulation for the management of dysphasia is still in its infancy. Fortunately, several research groups are moving to clinical trials to demonstrate the efficacy of first generation systems and have been demonstrating success in preliminary trials. Within the next 10 years, there is a good chance that FES and neuromodulation will be part of the standard of care in the management of dysphagia.

Conclusion

Swallowing is a complicated process controlled by several brain centers involving the intricate coordination of many muscles of the head and neck. Disruption to any of the CNS control centers results in some form of dysphagia or difficulty in swallowing. Many cases are resolved with rehabilitation and therapy with a speech and language pathologist. More involved cases, especially those in which the secretions cannot be controlled and result in chronic aspiration, require advanced intervention.

The standard practices include nil per oral (NPO) and PEG-tube, tracheostomy, and/or surgical manipulation to permanently separate the airway and foodways. Each of these is static, invasive, and somewhat destructive and nearly always accompanied with a decreased quality of life. Electrical stimulation is emerging as a dynamic treatment alternative. Neuroprostheses are being developed that restore either laryngeal elevation or vocal fold closure. In early clinical trials, these devices have demonstrated the potential to reduce aspiration. Within five to ten years, neuroprostheses should be a standard of clinical care for patients that have unresolved dysphagia following standard therapy, but prior to more extensive surgical interventions.

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Management and rehabilitation of neuropathic bladder in patients with spinal cord lesion

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Summary

The patients with spinal cord lesion (SCL) develop problems of urination due to impaired neural control of the lower urinary tract, such as incontinence or retention; these conditions constitute risks for the upper urinary tract and should be treated appropriately over the various phases of the disease. The therapeutic approach in the acute and subacute post-traumatic phase is of particular importance for the early and late management of the subsequent urinary disturbances. When the rehabilitation program is completed, it is estimated that deficiencies in sphincter control have greater impact on personal and social life of individuals than the movement disability. Currently, as the number of sufferers from SCLs is constantly increasing, medical science faces two great challenges: (i) to develop and apply modern treatment modalities in the framework of advanced neurorehabilitation programs, and (ii) to provide well-organized follow-up management. All efforts should be directed towards the functional integrity of the upper urinary tract and the acquirement of the greatest possible independence for the patient.

Keywords: Neurogenic bladder; neuropathic bladder; spinal cord lesion; spinal cord injury; neuromodulation; rehabilitation.

Introduction

The spinal cord lesions (SCLs) due to trauma or other pathology affect not only the mobility of the trunk and limbs but the function of the autonomous nervous system as well, and hence, they disturb the function of the internal organs. The visceral sympathetic nerves emerge from the thoracic and lumbar myelotomes; therefore, spinal cord lesions may interfere with sympathetic innervation. Visceral parasympathetic innervation is not affected, given that it bypasses the spinal cord via the vagus nerve. Internal organs such as the distal part of large intestine and the lower urinary tract receive autonomic neural inputs from the sympathetic thoraco-lumbar and parasympathetic sacral spinal nuclei; thus, they may be severed in cases of spinal cord damage. Our understanding of the role of the nervous system in the control of the lower urinary tract has been hindered by the following problems: 1) current electrophysiological techniques have limitations in their practice, 2) the functionality of the nervous system varies between anesthetized, alert, and neurologically impaired animals, 3) the simplified description of the neural circuits, which is acceptable for educational purposes, is not a sufficient theoretical platform on which to base treatment approaches, and 4) current knowledge and understanding are sufficient with respect only to the peripheral and spinal control of the lower urinary tract and not to the cerebral control.

Neural control of urination

The supraspinal central nervous system (CNS) control is associated with the augmentative or inhibitive action on the spinobulbospinal reflexes [28]. The levels of control can be divided as follows:

- High level: cerebral hemispheres, septal region, hypothalamus
- Intermediate level: midbrain (pontine reticular formation), hindbrain (cerebellum)
- Low level: spinal cord.

The superior frontal gyrus and the septal region appear to be the most important cerebral regions for the control of the detrusor muscle. The supracallosal gyrus and the limbic cortex are associated with the behavioral aspect of urination; in humans, these may not have the significance they have in animals, given that the latter use urine to mark their areas of predominance. The paracentral

lobule represents the cortical center for the pelvic floor muscles [28].

In the peripheral nervous system (PNS), two are the main components, which are involved in the mechanism of urination:

- the autonomous nervous system, sympathetic and parasympathetic (hypogastric and pelvic plexus), and
- the somatic nervous system (pudendal nerves).

Motor innervation of the bladder

The main motor innervation of the detrusor muscle comes from the parasympathetic fibers of the anterior second to fourth sacral roots (S_2–S_4). In the majority of humans, the S_3 root predominates [6, 8]. The compliance of the bladder decreases when only the anterior sacral roots are divided. A relevant finding in animals is an increase in the number of the adrenergic receptors [27]. If the posterior sacral roots are severed, a significant decrease in detrusor motility follows, whereas the bladder compliance increases. The efferent sympathetic pathways (preganglionic fibers) originate from the thoracolumbar region and may:

- synapse upon ganglion cells of the sympathetic chain; few postganglionic fibers reach the hypogastric nerves, while other connect to the pelvic nerves
- synapse within the inferior mesenteric ganglion via the ganglia of the sympathetic chain without intermediate synapses; in turn, post-ganglionic fibers follow the hypogastric nerves
- pass through the ganglia of the sympathetic chain without intermediate synapses, and synapse upon gaglion cells near or within pelvic organs via the hypogastric nerves, from which short postganglionic fibers arise.

Sensory innervation of the bladder

The visceral sensory innervation of the bladder is served from baroreceptos and pain receptors of the bladder, urethra, and rectum through Aδ and C fibers of the hypogastric and pelvic nerves. The somatic sensory innervation from the urethra and the pelvic floor runs through the pudendal nerves and conveys pain, thermal and nociceptive inputs. In particular, the passage of urine through the urethra is perceived by the pudendal nerves. Afferent pathways are connected to the following three categories of spinal cord neurons [6, 17]:

- local sacral intermediate neurons, which are associated with sphincter reflexes (after a SCL, they undertake the principal role in the reflex arch via the C fibers)
- lumbosacral neurons with short afferent neuraxons, which are associated with cysteo-sympathetic reflexes
- neurons with long afferent neuraxons (long sensory tracts), which pass through the brain stem and may involve spinal-bulbo-spinal reflexes.

The intermediate neurons may receive afferent inputs from the bladder, the rectum, the external genitalia, as well as visceral and somatic pathways.

Physiology of urination

The kidneys produce urine continuously; its rate of secretion, however, may be influenced by several factors: fluid intake, perspiration, blood pressure, cardiac output, and hormonal factors. Both passive and active mechanisms affect the transfer of urine from the kidneys to the bladder. The infiltration pressure inside the kidney (proximal convoluted tubules: 14 mmHg, renal pelvis: 6.5–11 mmHg, relaxed ureter and bladder: 0–6 cm H_2O) contributes to the passive downward movement of the urine. Additionally, the active peristaltic movements of the small calyces, renal pelvis, and ureters extrude the urine towards the bladder; this is achieved by primary pacemakers located in small calyces and secondary ones located along the ureter's wall. The secondary pacemakers are mainly driven by the primary ones, but they are still capable of producing a peristaltic wave. Normally, the expulsion of the urine from the kidneys to the bladder is achieved by peristaltic waves (2–6 waves/min with a velocity of 2–5 cm/sec) [12].

In 1968, DeGroat and Ryall, studied with quantitative electrophysiological techniques the reflexes, which control the function of the bladder and in fact, led the foundations of modern neurophysiology of the lower urinary system [5, 6]. Both urination and urine retention result from complex, sophisticated anatomical and physiological processes. The detrusor muscle contraction is caused by the stimulation of the parasympathetic system; pathways originating from the sacral centers of urination located at S_1 to S_4 myelotomes extend to the lateral horns of the spinal cord. Relaxation of the perineum elicits the perineal-bulbar stimulating reflex, which, in turn, signals the beginning of urination [12, 15, 17]. The baroreceptors of the perineal muscles stimulate suprasacral centers, which, in turn, stimulate the sacral centers of urination. The sympathetic system basically acts at the bladder neck, inhibiting the detrusor muscle through the sympathetic inhibitory reflex of the detrusor muscle. The beginning of urination occurs voluntarily, although its continuation relies on automated activity. Urination

may start almost independently of the volume of urine inside the bladder. Once higher centers trigger the spinal-bulbar-spinal reflex, local networks assume control of urination. The inputs from the baroreceptors of the bladder are mostly responsible for alerting the urination reflex.

Levels of nervous system lesions and urination control

When the communication between the higher cerebral and pontine centers of urination and the lower spinal centers (thoracolumbar sympathetic, sacral parasympathetic, and somatic nuclei) is interrupted, the function of lower urinary tract is severely affected. According to the level of the lesion within the nervous system, the following categories are recognized [28]:

- *Suprapontine lesions*: the voluntary inhibition of urination is disturbed and involuntary voiding/incontinence with coordinated sphincter function ensue.
- *Supra-sacral lesions*: after the period of spinal shock, bladder and sphincter dyssynergia and involuntary reflex voiding develop.
- *Lesion at sacral nuclei*: bladder is paralysed and contracts weakly in an autonomous fashion by the remaining intramural gaglionic innervation. If the thoracolumbar sympathetic nuclei are not severed, a degree of continence may remain.
- *Lesion of the peripheral motor innervation of the lower urinary tract*: the bladder presents small capacity and decreased compliance, and the number of the adrenergic receptors increases.
- *Lesion of the peripheral sensory innervation of the lower urinary tract*: areflexic bladder of increased capacity and compliance.
- *Decentralized bladder:* only in cases of congenital absence of the intramural ganglia (megacystis).

The voiding reflexes after a spinal cord lesion

The condition following a SCL is characterized by complete paralysis of the bladder lasting for a variable period of time (''spinal shock''). The synapses of the motor neurons of the detrusor muscle with descending tracts distally to the lesion are abolished; local axonal sprouting substitutes their function after a considerable time interval. This reorganization is a phenomenon of neuroplasticity. The ''spinal shock'' reflects complete loss of neural functions below the level of the lesion and implies that suppression of the somatic reflexes and flaccid paralysis coexist. The ''spinal shock'' may also affect the activity of the autonomous nervous system; however, the detrusor muscle may remain atonic while the reflexes of the conus medullaris continue to be elicited [2, 4, 22].

Recovery from the spinal shock requires a variable period of time. The late reactivation of the parasympathetic response of the detrusor muscle may be attributed to various factors such as muscle lesion of the detrusor due to overdilation, overactivity of the sympathetic against the parasympathetic system, persistent state of spinal shock, and mixed lesion of the conus medullaris (selective damage of the detrusor's sacral nuclei while the sacral nuclei of Onuf remain intact).

In spinal cord lesions, innervation of the descending colon and rectum may also be affected; however, most of the sufferers manage to control defecation following intensive programs of voiding. The parasympathetic system running via the vagus nerve, the intestinal myenteric, and the submucosal nervous system contribute to the preservation of adequate bowel function. The portion of the large bowel distally to the descending colon receives neural inputs from spinal centers as well; this explains why its function is variably affected. The defecation disorders do not constitute a major problem during the early rehabilitation phase in patients suffering from spinal cord damage; it appears that this type of disturbances aggravate progressively as time passes from the original impact. Both urination and defecation are neurologically controlled at the same levels of the spinal cord, while common reflexes (ortho-cystic) ensure the effective coordination of the above functions. Although neurogenic bladder can be associated with neurogenic bowel, the latter entity is beyond the scope of the present article.

Types of neuropathic bladder

The types of neuropathic bladder following spinal cord lesion are determined by urodynamic, imaging, and electrophysiological studies. According to the International Incontinence Society (ICS) [1] and the Madersbacher classification system [14], the following four main types of neuropathic bladder can be recognized (Fig. 1):

1. neurogenic overactivity of both the detrusor muscle and the urethral sphincter mechanism
2. neurogenic underactivity or inactivity of both the detrusor muscle and the urethral sphincter mechanism

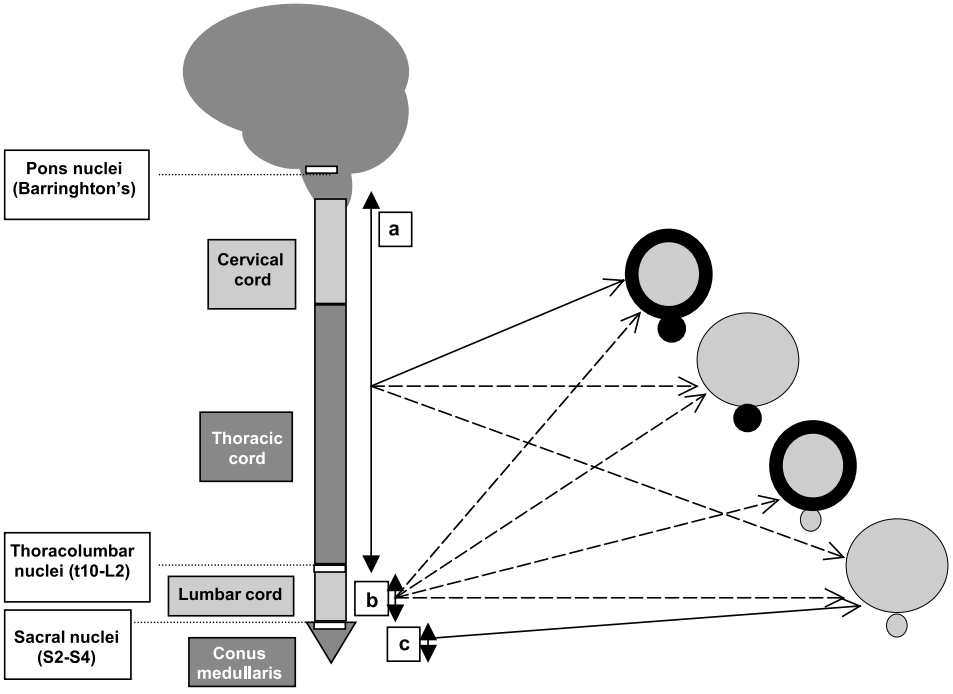

Fig. 1. Types of neuropathic bladder in SCL according to the level of injury: (*a*) cervical and thoracic cord lesions, (*b*) lumbar cord lesions, and (*c*) sacral cord lesions (grey color represents underactivity and black color overactivity)

3. neurogenic underactivity or inactivity of the detrusor muscle and neurogenic overactivity of the urethral sphincter mechanism
4. neurogenic overactivity of the detrusor muscle and neurogenic underactivity of the urethral sphincter mechanism

Any specific type does not correspond to a specific level of spinal cord lesion; all types may be present at any level of spinal cord lesion, instead [22]. The paradox variance between the type of neurogenic bladder and the level of the spinal cord lesion may be attributed to several factors such as the existence of a second lesion at another level of the spinal cord or the presence of spinal shock. Factors associated with autonomous nervous system may also interfere with the clinical presentation; such parameters may be the myogenic lesion of the detrusor muscle due to bladder overdistention and the degree of the spinal cord damage i.e. complete versus incomplete etc. In our Neuropathic Bladder Unit of the National Rehabilitation Center, 167 patients with traumatic SCLs were evaluated. It was demonstrated that the level of spinal cord damage does not correspond to any specific type of neuropathic bladder. The patients were studied after their recovery from the spinal shock based on the presence of the anal reflexes. Each type of neuropathic bladder was determined by specific urodynamic studies, dynamic retrograde cystography, and electrophysiological studies (Fig. 2).

Dyssynergia

In this condition, both the detrusor muscle and the sphincter muscles of the urethra are simultaneously and involuntary contracted. During urination, the pontine centers are responsible for the coordination of the detrusor muscle and the sphincter mechanism. Dyssynergia is a neurogenic voiding disorder, in which the pathways from the pontine to the spinal centers of urination have been interrupted; the spinal cord lesion constitutes a characteristic paradigm of the damage. Although various types or subtypes of dyssynergia have been described, two are the most important clinically: the continuing dyssynergia, which is particularly risky for the upper urinary tract, and the intermittent dyssynergia with simultaneous incontinence [20, 25, 26, 30].

Management of neuropathic bladder: safe voiding

The effective treatment of the neurological disorders of urination which are secondary to SCL has dramatically reduced the mortality rates because of severe renal damage. At the beginning of the 20th century, mortality

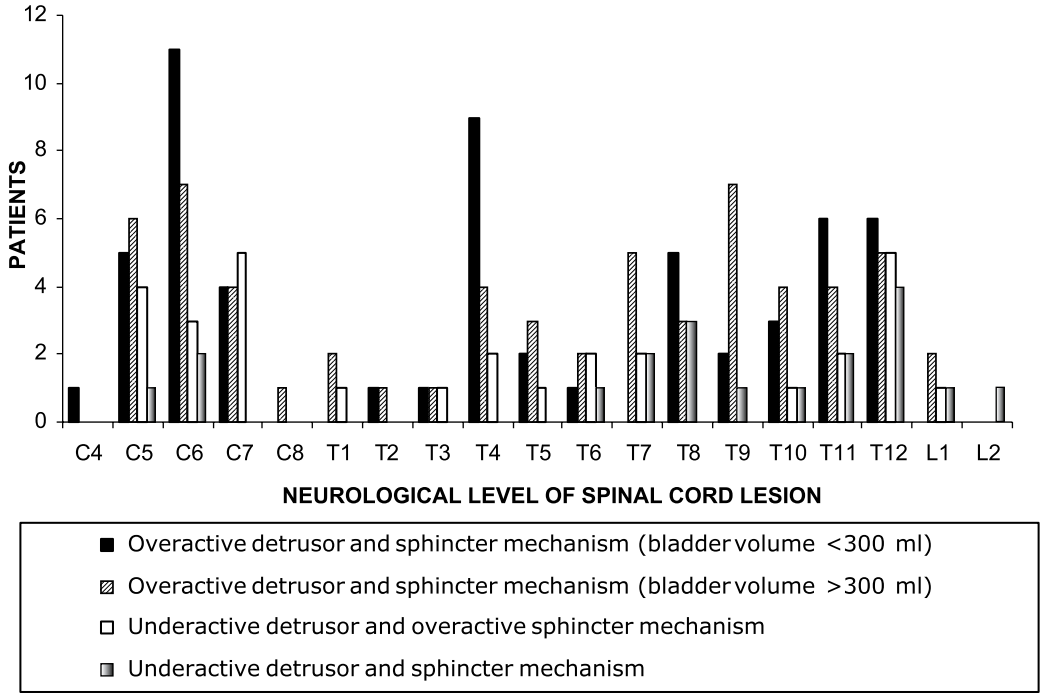

Fig. 2. Distribution of the patients ($n = 167$) according to the type of neuropathic bladder they developed and the level of the spinal cord injury (Neuropathic Bladder Unit, National Rehabilitation Center, Greece)

of SCL due to renal complications was as high as 95%, whereas it has currently been lowered to 3%. The following factors have contributed to this impressive improvement [10, 13, 21]: 1) intermittent catherizations of the bladder, 2) avoidance of indwelling catheters, 3) improved management of urinary infections and urolithiasis, 4) modern urodynamic studies, 5) special outpatient clinics, and 6) long-term follow-ups. Several methods of bladder management are available in the post-acute phase of SCLs. The selection of a method should aim in producing a continent bladder with adequate low-pressure storage capacity. Ideally, the selected method should ensure that: 1) the bladder fills and empties under secure conditions for the upper urinary tract; adequate compliance and capacity, as well as intravesical pressure lower than 40 cm H_2O are essential goals of management, 2) potential complications such as vesicoureteral reflux, lithiasis of the bladder or recurrent symptomatic urinary infections should be avoided or detected and treated as soon as possible, 3) the bladder is continent with a capacity greater than 300 ml; additionally, continent intervals should last at least 3–4 hours, and 4) the patient remains self-dependent.

For the above aims to be achieved, the following conditions should be managed: 1) the detrusor overactivity with administration of oral anticholinergic agents (oxybutinin, tolterodine etc) or botulinum toxin A (BTX-A) injection to the detrusor muscle during cystoscopy, 2) the proximal urethral sphincter overactivity with oral α-blockers agents or sphincterotomy, 3) the distal urethral sphincter overactivity with oral medications (baclofen, dantrolene) or transperineal or transurethral local BTX-A injection, and 4) the detrusor underactivity with oral medications (betanechol etc) or intravesical electrostimulation. The treatment of sphincter urethral underactivity with oral medications was associated with low success rates in the past, mainly due to side effects. In incomplete lesions, programs aiming to re-educate the pelvic floor muscles include exercises, biofeedback, and electrostimulation. When conservative management programs fail, the surgical implantation of an artifical sphincter represents the best possible treatment. Vesicuolureter reflux (VUR) has been one of the most severe side effects [19], given that it sets in risk the upper urinary tract (Fig. 3). In our series of 167 patients with SCL, 11 (5%) developed VUR; this was more common in the following subgroups of patients: a) SCLs below T11 myelotome, b) incomplete SCLs, c) patients with urodynamic findings of dysynergia, and d) when the interval between impact and first appointment in Neurogenic Bladder Outpatient Clinic was longer than 2 years.

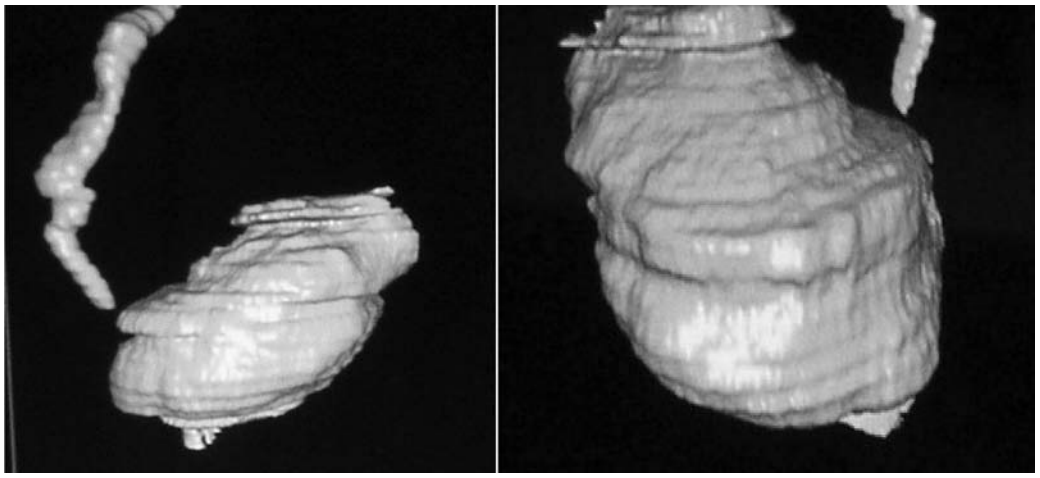

Fig. 3. Spiral CT (retrograde cystography): overactive neuropathic bladder with reflux in a 38-year-old man with SCL (fracture in 10th thoracic vertebra)

Rehabilitation of neuropathic bladder in patients with SCL

An effective ''rehabilitation program of neuropathic bladder'' should take into consideration not only the aims mentioned in previous sections, but the coexisting movement disorders, sensory disturbances, and spasticity. For example, a patient with tetraplegia secondary to a high cervical damage (e.g. at the C7 myelotome) manifests complex neurological disorders; their management requires an integrated approach. The sufferer cannot move the flexors muscles of the fingers and the muscles of the hands and his grasping ability is greatly impaired. In order the patient to empty his bladder with intermittent self-catherizations, physical tenodesis or tendon tranfer to the flexors muscles of the fingers and systematic occupational therapy interventions are needed. The electrical stimulation of the anterior sacral roots with dissection of the posterior sacral roots appears to be an effective therapeutic approach in patients with SCLs, particularly when grasping disturbances and autonomic dysreflexia attacks coexist [11]. Sacral anterior root stimulation (SARS) needs, however, certain criteria to be met: adequate reflective contraction of the detrusor muscle (>50 cm H_2O in men, >35 cm H_2O in women), bladder capacity more than 200 ml, and complete SCL (given that the posterior sacral roots should be divided). Recently, a new surgical technique, the SPARS (sacral posterior/anterior root stimulation), has given promising results when both anterior and posterior sacral roots are stimulated without posterior sacral roots being sacrificed. This procedure may prove particularly helpful in cases with incomplete SCL. In modern neurorehabilitation programs, another main concern is the management of coexisting spasticity; this makes difficult or impossible the intermittent bladder catherizations, as well as the patient's transfer from the wheel-chair to the toilet. In such cases, spasticity may be treated with oral or intrathecal administration of drugs (baclofen) or other drug combinations.

Illustrative case

Undeniably, the effective management of neuropathic bladder secondary to SCLs requires an integrative approach to the problem. We briefly report the characteristic case of a 38-year woman, who experienced a traumatic complete sensorimotor paraplegia due to damage at T9 myelotome. The patient presented with profound spasticity of the lower limbs and abdominal muscles, and difficulty in abduction of her thighs; these findings altogether impeded the ability for self-catherization and transfer, while falls from the wheel-chair were common. High doses of anticholinergic drugs (15 mg oxybutinin/day) were administered to control overactivity of the detrusor muscle, although one to two attacks of incontinence per month were reported (reflex volume: 300 ml, intravesical pressure due to detrusor contraction (P_{det}) at reflex volume: 65 cm H_2O). The oral administration of baclofen (up to 90 mg/day) and dantrolene (150 mg/day) was not effective. Eight years following her accident, the patient underwent subcutaneous implantation of a pump for intrathecal injection of baclofen. Following a short period of hospitalization, the daily dose of baclofen was optimized at 300 μg/day and the patient begun to re-approach everyday activities setting new higher standards; the degree of spasticity

(assessed by the modified Ashworth scale) decreased from the 3/4 (preoperatively) to the 1/4 (postoperatively) in most muscles of lower limbs (3). The postoperative doses of anticholinergic medication were reduced to 10 mg oxybutinin/day with adequeate detrusor control (reflux volume: 350 ml, P_{det} at reflex volume: 35 cm H_2O). The patient became fully continent and self-dependent in terms of transfer to the toilet and self-catherizations.

Complete spinal cord lesions and management of neuropathic bladder

A SCL may be complete or incomplete as this can be determined by clinical or laboratory criteria; it may also disrupt the efferent or afferent neural pathways (incomplete motor, incomplete sensory), and the somatic or autonomous nervous system. The clinical evaluation of the somatic nervous system is based on advanced measurement scales such as the American Spinal Injury Association (ASIA) [7, 16].

Both bladder proprioception (sense of filling) and exteroception (electrical input sensation) do not always correspond to complete SCLs [29]. Moreover, the somatic sensory pathways do not coincide with the visceral sensory inputs of the autonomous nervous system [23]. Combined electrophysiological and urodynamic studies may indicate accurately the neurogenic disorder of the lower urinary tract and be used as prognostic factors in cases of thoracic, lumbar, or multilevel SCLs [21, 24]. The preservation of pinprick sensation in lower sacral neurotomes 4 weeks after a SCL has also been reported as a good prognostic factor in terms of walking ability [18]. In respect to the urination control, however, pinprick sensation has not always been associated with favorable outcome; nevertheless, all sufferers who experience normal control of their urination had preserved pinprick sensation [24]. The initial clinical and electrophysiological assessments are mandatory for the prognosis of the SCL impact in somatic nervous system, which innervates the lower urinary tract; however, this evaluation does not always indicate the type of urodynamic disturbance [3]. Complete lesions are usually associated with continuous spasm of the external sphincter [24, 26, 30], while incomplete lesions present somewhat benign types of dyssynergia. Given that dyssynegia appears to deteriorate over time, close follow-ups and regular assessments are of great importance [25]. It has been reported that patients with complete SCL manifest more attacks of autonomic dysreflexia during their recovery period compared to patients with incomplete lesions. Interestingly, sufferers of incomplete motor lesion are in risk of presenting autonomic dysreflexia at a later stage (1–6 months post-injury) [9].

Incomplete spinal cord lesions and management of neuropathic bladder

In incomplete SCLs, the recovery of lower urinary tract function becomes more difficult when: a) increased spasticity coexists, b) the therapies for neuropathic bladder are not approved by the patient because they could interfere with existing ''satisfactory'' motor ability in other parts of the body, c) copious walking jeopardizes upper urinary tract function, d) long-term neuropathic bladder disorders develop e.g. deterioration of dyssynergia and e) the patient may not accept to participate over the prolonged follow-up periods needed. On the other hand, the management of neuropathic bladder following incomplete SCLs becomes easier when: a) a degree of sensation remains during urination, and b) there is mild degree of dyssynergia. Much progress has been made in the field of neuropathic bladder disorders after SCLs in terms of diagnosis and clinical management. However, critical issues have not been resolved. Few of them are listed below: 1) How objective is the clinical assessment of sensitivity, particularly, in cases of partial loss of sensory control? 2) Are electrophysiological results the preferable and most effective way for the categorization of patients? 3) How important is the evaluation of the autonomic nervous system and visceral innervation in the global neurological assessment after a SCL? 4) When the degree of lesion in the autonomous nervous system is known, can we be more effective in the management of neuropathic bladder and control of autonomic dysrflexia? Accumulated data over the last few years suggest that, in the foreseeable future, the lesions of the spinal cord will be divided in the following two categories: a) somatosensoric complete/incomplete lesions, and b) viscerosensoric complete/incomplete lesions.

Concluding remarks

Urination in human adult constitutes a fully controlled function and keeps pace with children's psychomotor development and sphincter control at the age of 4 years. Any urination disorder in adult life has a great somatic and psychological impact for the sufferers. A variety of studies have been conducted to evaluate the functional performance of patients with SCLs at the end of their

rehabilitation programs; it has been clearly shown that disorders in sphincter control affect more dramatically their quality of life compared to the residual movement disabilities. Follow-up assessments as part of elaborate rehabilitation programs and advanced methods for the management of neuropathic bladder in patients with severe SCLs are mandatory for acquiring adequate urination control and ensuring safety of the upper urinary tract. Currently, neurorehabilitation faces two big challenges: firstly, to help the patient to achieve the greatest self-dependency of the sufferer in terms of bladder emptying and secondly, to organize follow-up programs on a systematic and productive manner for such patients. Recent data advocate that even tetraplegic patients with severe disabilities of grasping, may expect an easier life thanks to the advances in current neurorehabilitation and neuromodulation practice.

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Sacral neuromodulation as a functional treatment of bladder overactivity

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Summary

Sacral neuromodulation, namely the electrical stimulation of the sacral nerves has become an alternative treatment for cases of idiopathic bladder overactivity. The mechanism of action in this type of spinal cord modulation is only partially understood but it seems to involve stimulation of inhibitory interneurons. Temporary sacral nerve stimulation is the first step. It consists of the temporary application of neurostimulation as a diagnostic test in order to check the integrity of the sacral root and determine the best location for the implant. If the test stimulation is successful, a permanent device is implanted. In experienced hands, this is a safe procedure. When the patients are selected on the basis of sound criteria, more than three-quarters of them show a clinically significant improvement with a reduction in the frequency of incontinence episodes by more than 50%; however, the results vary according to each author's method of evaluation. The application of this technique should be combined with careful follow-up and attentive adjustments of the stimulation parameters in order to optimize the coordination of activity between the neurological systems involved.

Keywords: Bladder; neurogenic; functional electric stimulation; voiding dysfunction; urinary urge incontinence; sacral root.

Introduction

Vesico-urethral dysfunction is a major problem in modern medical practice because it is associated with psychological consequences, social costs and a serious impact on the quality of life. A complex neuroanatomical network controls the coordination of spinal, pontine and supra-pontine centers, with vegetative and somatic systems in order to regulate the urinary function. Regardless of this complexity, the consequences of dysfunction in any part of the network are the same, i.e. retention and subsequently overfilling-related emptying of the bladder in order to ensure continence and protection of the upper urinary tract. Surgical techniques intervening with the peripheral or central nervous systems have always played an important role in the restoration of this function. Recently, sacral neuromodulation, namely the electrical stimulation of the sacral nerves, appears to have become an effective alternative to radical bladder surgery.

Overactive bladder (OAB)

Definition

According to the International Incontinence Society, the definition of bladder overactivity generally involves all symptoms related to urinary urgency, with increased daily frequency (polyuria) or night-time (nocturia) micturition with or without incontinence [1]. This can be recorded on a micturition calendar that allows registering number of micturitions, volume, episodes of incontinence, use of protective measures, etc. This calendar enables the therapist to assess the gravity of the disorder and its impact on the quality of life. This definition, however, has the limitation that it does not take into account the whole ''neurological'' patient. Notably, the definition of bladder overactivity can be related to the patient's urodynamic status. The bladder is considered ''hyperactive'' when it contracts spontaneously, in response to stimulation, during the phase of filling or when the patient is incapable of preventing contractions. The diagnosis of bladder hyperactivity is made when the uninhibited contractions have an amplitude of at least 15 cm H_2O. The urodynamic check-up is informative when it shows involuntary contractions of the detrusor, regardless of the amplitude during the filling phase. Furthemore, the urodynamic examination is useful in: a) the evaluation of ''rebel overactivities'', b) assessment and management of repercussions on the upper urinary

tract, c) as an adjunctive test to other examinations, and d) in the check-up carried out before invasive therapies.

Etiology

We tend to classify bladder overactivity into two major categories: a) neurogenic hyperactivity or hyperreflexia of the detrusor, and b) idiopathic hyperactivity or instability of the detrusor [14]. The numerous causes of bladder overactivity are described below:

a) Central nervous system conditions (traumatic, demyelinating, cerebral vascular accidents, tumours, hydrocephalus, degenerative illnesses, Parkinson's disease, etc.)
b) Obstructions of the urinary tract flow
c) Hypersensitivity of the detrusor of any cause (such as interstitial cystitis)
d) Idiopathic hyperactivity without a recognisable cause

Bladder overactivity represents not only a functional handicap, but also a risk to life when the bladder pressure becomes high (vesico-urethral reflux) or recurrent urinary infections occur which can affect the upper urinary tract and cause renal insufficiency, pyelonephritis, septicaemia, etc.

Treatment of OAB

Medical treatment

In patients in whom the perineal sensation has been preserved, perineal re-education to stimulate the afferents and provoke central inhibition can be tried, although the clinical results, so far, have been disappointing [4]. The pharmacological treatment is based on anticholinergic drugs, which act on the bladder's soft muscle, but their frequent side-effects often limit their use.

Intravesical agents

When these treatments fail and the upper urinary tract remains threatened, intravesical agents represent a good alternative. The aim of the *intradetrusor botulinum toxin* (*Botox*^{TM}) injection is to paralyse the smooth muscle of the bladder. The efficacy of the treatment can be observed by the increase of the functional bladder capacity and the reduction in the number of daily episodes of incontinence. The objective of the technique is a state of reduced contractility of the detrusor; this requires carrying out repeated catheterizations [17]. The duration of the results on incontinence (6–9 months), necessitate re-injections by endoscopic methods. At present, we do not have sufficient follow-up to assess possible secondary leaks; nevertheless, it is a promising technique, which is used in many countries. Intravesical instillations of vanilloids (*capsaicin*, *resiniferatoxin*) allow a specific neurotoxic agent of the C fibres to be liberated within the bladder. The activity of C fibres is considered to be at the origin of bladder hyperactivity. Finally, when micturition capacity is insufficient, repeated catheterizations should be proposed for protection of the upper urinary tract and reduction of incontinence. These techniques, however, are undergoing clinical evaluation [9].

Urological treatment

Bladder enlargement or enterocystoplasty consists of opening the vesical globe and adding, as a ''patch'', a detubulised small intestine segment. This is a complicated surgical technique that requires repeated catheterizations to be carried out. The results are good with respect to continence (70–80% of the patients), but in over 50% recurrent urinary infections do occur and 22% of the cases are complicated by the formation of urinary calculus [13].

Treatment of OAB by interventions on the nervous system

The techniques that interfere with the central or peripheral nervous system in order to restore bladder function have always occupied an important place in neurourology; this is true not only with respect to their underlying concepts but also to the necessary techniques for performing them.

Historical background of sacral neuromodulation

In 1981, Tanagho and Schmidt embarked on a project comparable to Brindley's program with paraplegic patients, i.e. extradural stimulations of the sacral roots to induce a contraction of the detrusor and subsequent posterior rhizotomies to suppress vesico-sphincter dyssynergia. Later on, they concentrated on stimulating at low intensity the S3 roots without damaging them, by percutaneous puncture. They obtained an inverse effect; the inhibition of the bladder contraction [20]. These results gave rise to the term sacral neuromodulation, i.e. the application of electrical stimulation at the sacral root level in order to modify the behaviour of a hyperactive

bladder. The first publications reported improvements in bladder hyperactivity in patients suffering from spinal cord lesions, but this method soon proved also effective in the treatment of idiopathic bladder hyperactivity. More recently, this technique has been demonstrated to be effective in the treatment of chronic urinary retention and in specific types of pelvic pain.

Historical background to other methods

a) *Electrical stimulation of the pelvic floor* has been used to treat incontinence. In 1963, Caldwell carried out the first implantation of a stimulator in the striated sphincter to treat incontinence in a patient. However, it was recognized soon that transrectal or transvaginal stimulation gave the same results. The mechanism of these stimulations is similar to that of sacral neuromodulation and to stimulation of the posterior tibial nerve (PTN).

b) *Sacral nerve deafferentation* aims to suppress the vesico-medullary reflex, which is responsible for bladder hyperreflexia and closely related to incontinence. The principle of sacral deafferentation was introduced a century ago with the aim to reduce spasticity. Specific C fibres are responsible to a great extent for the self-maintenance of the phenomenon [24]. Rhizotomies can be carried out at conus medullaris, intradurally at the lumbar region and at the radiculo-medullary junction or Dorsal Root Entry Zone (DREZotomies) [21]. These deafferentations are offered to paraplegic or tetraplegic patients and, in general, are combined with stimulation of the anterior roots (Brindley's method). Sacral alcoholisations are not recommended because they are responsible for serious undesired effects. Thermocoagulation of the sacral roots in their foramen aims at destroying the thermosensitive C fibres while simultaneously preserving the other sensory and motor fibres; hence, it would be a less invasive alternative for treating bladder hyperreflexia. This technique, however, needs to be repeated several times.

c) *Posterior tibial nerve (PTN) stimulation* is now a therapeutic method, which is reversible and non-invasive. It is based on stimulating the PTN of the ankle transcutaneously by adhesive electrodes. This nerve contains lumbo-sacral fibres, which participate in the lower urinary tract innervation. Stimulation is carried out continuously for twenty minutes a day over 12 weeks (10 Hz, 200 μs, below pain-threshold intensity). The mechanism of action is highly debatable. Stimulation may either induce a central inhibition of the pre-ganglionic vesical motor neurons or exercise a direct action on the lemniscal tracts of the dorsal medial column [22]. The effectiveness of acute stimulation on bladder activity has been proved by both urodynamic (functional bladder capacity and set-back of volume of reflex urination) and clinical evaluations, with 50% of patients who received this type of treatment giving a successful response [2].

d) *Transcutaneous magnetic stimulation (TMS)* was introduced in the 1980's. It has the advantage of being less invasive and accurate enough in stimulating both anterior and posterior sacral roots in their foramen as medullar segments [6]. In bladder hyperactivity, TMS has been shown to be effective in reducing the symptoms. However, for TMS to be effective, it must be applied at the sacral foramen level every day for a considerable period of time, a requirement that undoubtedly limits its use. Nevertheless, it can be proposed as a test which may predict efficacy of other treatments including PTN stimulation or sacral neuromodulation.

e) *Pudendal nerve stimulation* has a beneficial impact on the cystometric parameters in a great number of patients with refractory detrusor instability. It may provide an efficacious treatment for patients suffering from urgency-frequency and urge incontinence associated with the overactive bladder syndrome. An implantable microstimulator weighting less than 1 gram is now available. Electronics, rechargeable battery and stimulating electrode are integrated into a single implantable device. The implantation is performed at Alcock's canal using a minimally-invasive technique under local anaesthesia and in an approach similar to the well-established transperineal pudendal block [11]. The patient needs to sit on a custom cushion for approximately 20 min a day to recharge the microstimulator through radio waves. The responsible clinician uses bidirectional telemetry to program the neurostimulator and retrieve information about the patient's use of the device. The patient uses the remote control to stimulate or to turn the microstimulator on and off. The long-term efficacy of this device needs to be confirmed in large clinical trials; nevertheless, it represents an alternative to sacral neuromodulation [18].

Pathophysiology of sacral neuromodulation

Currently, the mechanisms underlying sacral neuromodulation are far from being well understood. This is due, in part, to the few existing animal models and the limited number of studies carried out on humans. Numerous theories have been proposed, but they are all controversial, as they lack objective scientific

confirmation. The most widely known theories are described below:

a) *Stimulation of efferents or direct effect on the muscle*. Although there is little evidence to support it, this theory is based on the fact that sacral neurostimulation acts on a mixed nerve that contains pudendal afferents and efferents. It is logical, therefore, to implicate the latter in the contraction of the striated sphincter and continence. Stimulation of pudendal efferents could increase the tone of the urethral striated sphincter or induce an inhibition of the destrusor reflex [20].

b) *Stimulation of the afferents*. It is known that stimulation of the afferent fibres of the perineal region (vagina, uterine neck, penis, perineum, pudendal nerve) can inhibit activation of the sacral interneurons normally involved in urination [8]. Vaginal electrical stimulations can cause an inhibition of bladder hyperactivity depending on the frequency of stimulation. With respect to the micturition reflex, we can produce facilitation by stimulating the urethral afferents and inhibition by stimulating the dorsal nerve of the clitoris, which interacts with the vagina. It is the opinion of several investigators that the inhibitions of bladder and urethral excitatory reflexes are associated. On the basis of this evidence, a sacral neuromodulation technique has been developed with the aim of treating bladder hyperactivity. This technique induces a presynaptic inhibition in the primary afferents or postsynaptic inhibition on the second-order neurons. In fact, postsynaptic inhibition can be achieved through stimulation of the pudendal nerve afferents and sacral stimulations can act in the same manner (Fig. 1).

c) *Induction of spinal neuroplasticity by chronic stimulation*. Peripheral electrical stimulation induces changes in the sacral spinal cord, and an increase in the c-fos expression. It is possible to influence the functional properties of the bladder reflexes in rats and mice by electrical stimulation. It has been proposed that segmental inhibition would be associated with amplification of the central micturition reflexes. The functional involvement of C fibres in the genesis of bladder hyperactivity seems to be important, while thicker fibres could be associated with stimulation-induced inhibition [25]. Chronic S1 stimulation in rats with bladder hyperactivity provokes a reduction in the expression of the TPRV-l receptors, which are charged by the C fibres. This finding, however, remains controversial. In humans, sacral stimulation modifies the bladder perception thresholds.

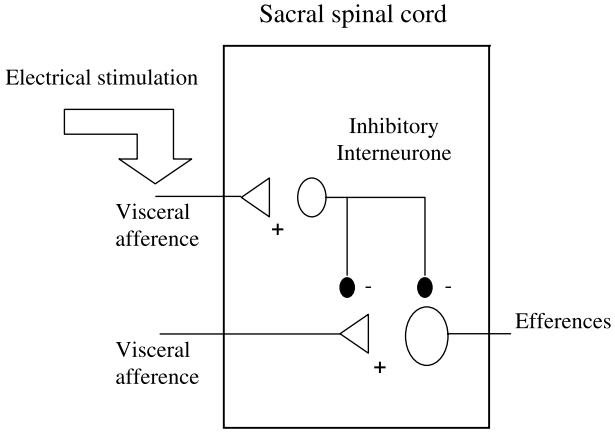

Fig. 1. Diagram showing the proposed mode of action of the sacral neuromodulation

d) *Cortical action*. Recently, many authors have proposed that sacral neuromodulation should have a suprapontine target, that is, cortical. In clinical practice, it has been shown that sacral neuromodulation is not effective in cases of complete spinal cord damage [12]; only patients with incomplete lesions of the spinal cord are capable of responding to this therapy [7]. Functional magnetic resonance imaging (fMRI) studies in humans have shown that, during sacral neuromodulation, different cerebral regions are activated, particularly in the motor cortex; this can last for several hours after the stimulation had ceased.

Clinical application of sacral neuromodulation

Indications

Neuromodulation of the sacral nerves is a therapeutic option for voiding problems due to dysfunction in reflex coordination between the bladder, sphincter and pelvic floor in patients who do not respond to the common non-invasive therapies. The rationale for using electrical stimulation in the treatment of voiding dysfunction is that stimulation re-adjusts the neurological control mechanism at a more functional status. The main indications are urge incontinence, and bladder overactivity (OAB) syndrome. OAB syndrome, which is also called urge syndrome or urgency-frequency syndrome, is characterized by urgency, with or without urge incontinence, usually with increased daytime frequency and nocturia, in the absence of local or metabolic factors, which could be responsible for these symptoms [1]. In patients suffering from OAB, sacral neuromodulation is an appealing therapeutic modality for symptoms refractory to conventional pharmacotherapy, and its use may be relevant to OAB of either neurological or non-neurological causes.

In patients suffering from chronic urinary retention, sacral neuromodulation should be reserved for functional urinary retention in cases without evidence of mechanical obstruction. Various other conditions such as Fowler's syndrome, spastic pelvic floor syndrome and bladder hypo/acontractility have been considered as potentially suitable for this treatment. Pelvic pain syndrome is characterized by persistent, recurrent episodes of pelvic pain associated with symptoms suggestive of lower urinary tract, sexual, bowel or gynecological dysfunction, without any obvious lesion [1]. Chronic pelvic pain is defined as the pain in the pelvic region with a minimum duration of 6 months that is not caused by any identifiable condition. In patients suffering from chronic pelvic pain, sacral neuromodulation techniques may be indicated if the symptoms are refractory to pharmacotherapy.

Evaluation

Before the implantation of a neuromodulatory device, each patient should undergo a thorough investigation in order to obtain baseline urodynamic values; these confirm that there is a proper indication and ensure that there are no contraindications. The pre-operative work-up for sacral neuromodulation must include careful assessment of previous medical history with particular attention on the use of drugs, which can influence bladder function, physical and neurological examination, and perineal examination with urodynamic assessment of bladder and sphincter function. In order to rule out any other lower urinary tract pathological conditions, the following test should be performed: a) urine culture to exclude urinary tract infection, b) cytology and cystoscopy to rule out carcinoma or cystitis, c) imaging of the upper urinary tract, and d) MRI of the entire spinal cord to check for diseases such as multiple sclerosis, neoplasms, syringomyela, lipoma, etc.

In the treatment of incontinence, the assessment of outcome is based on the use of a voiding diary for recording the number of episodes of incontinence and micturition. Recording the mean number of pads used every 24 hrs may be also helpful, and if possible the quantification of the amount of urine lost in the pads [3]. The severity of the symptoms can be recorded in a validated Urinary Incontinence Outcome Score, such as the Urological Distress Inventory, the Bristol Female Lower Urinary Tract Symptoms Questionnaire or the Incontinence Impact Questionnaire [21]. Many scores such as the Short-Form-36 (SF-36) and Beck depression inventory (BDI), may be used to evaluate the repercussion of incontinence on the quality of life. If there is no correlation between the severity of OAB symptoms and the urodynamic parameters of detrusor overactivity, most authors recommend the use of cystometry to evaluate the response to sacral neuromodulation. The *maximum cystometric capacity* (volume at which the patient feels that can no longer delay micturition), the *reflex volume* (volume at which the first uninhibited contraction of the detrusor occurs), the sensation of bladder filling and the degree of *bladder compliance* (relationship between change in bladder volume and change in detrusor pressure) may reflect the extent of bladder activity.

Surgical approach

Patients undergoing sacral nerve stimulation must go through the three phases of this therapy.

Phase 1 or "*acute phase*" involves a percutaneous test stimulation; a temporary electrode is placed in the third sacral (S3) foramen and connected to an external pulse generator.

Phase 2 or "*sub-chronic phase*" follows the acute phase. It involves monitoring and adjusting the external pulse generator to identify the optimal comfort level of stimulation and to evaluate therapy.

Phases 1 and 2 are dependent on an external generator and are considered as peripheral nerve evaluation (PNE).

In *phase 3* or "*chronic phase*", a permanent device is implanted.

Peripheral nerve evaluation (Fig. 2)

The first phase, i.e. temporary sacral nerve stimulation is the first step and aims to check for the integrity of the

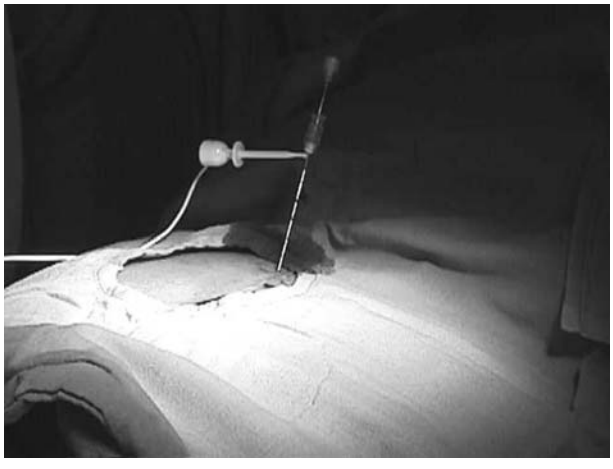

Fig. 2. The percutaneous test

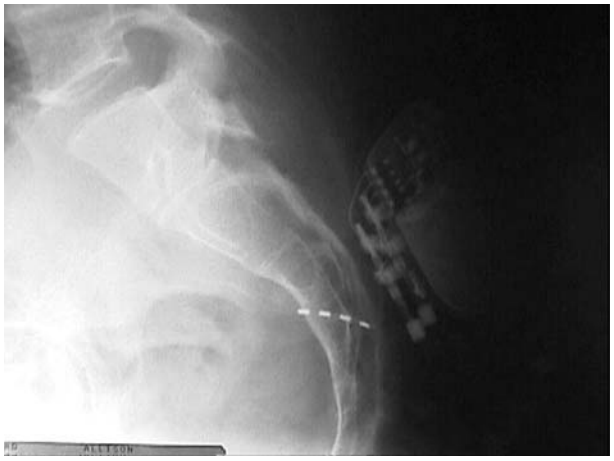

Fig. 3. Radiograph disclosing the final position of the implanted device

sacral root and to determine the best location for the implant. This stage is important because many technical difficulties can arise that should be dealt with in this stage.

In most patients, stimulation of the S3 sacral nerve yields optimal results. The stimulation of S3 root can elicit the following typical responses: contraction of the levator ani muscles, causing a ''bellows'' contraction of the perineum (deepening and flattening of the buttock groove); plantar flexion of the big toe (and sometimes other toes) due to sciatic nerve stimulation and paresthesia in the rectum, perineum, scrotum or vagina.

Implantation of neurostimulator (Fig. 3)

The permanent lead has four electrodes and a large stimulation zone. Special control equipment is used to adjust the stimulation parameters which generally are: amplitude 0.1 volts, frequency 10–14 Hz, and pulse width 210 μsec. The optimal nerve responses are identified, the distal end of the lead is anchored to the lumbodorsal fascia and the lead is connected to the extension electrode and to the neurostimulator that is placed in a subcutaneous pocket in the upper buttock or in the abdomen. Recently, a new minimally invasive technique was reported; this is characterized by a percutaneous approach to the sacral nerves allowing the patient to remain awake during the electrode placement [19]. During the percutaneous test, under local anesthesia, it is possible to place a quadripolar lead, which has a markedly reduced risk of an inconclusive stimulation response. If the test stimulation is successful, the internal pulse generator (IPG) can be implanted and connected under local anesthesia.

Results in OAB syndrome

The efficacy of sacral neuromodulation procedures can be assessed by objective and subjective measures. However, the subjective measures are difficult to implement because the patients' definitions tends to vary substantially when compared to the actual improvement that occurs in them. For review see Vignes et al. [21]. A multicenter randomized controlled trial of sacral nerve stimulator implantation in 34 patients with a six months follow-up was reported [16]. Approximately, three-quarters of the patients showed a clinically significant improvement with 50% reduction in the frequency of episodes of incontinence. There was an improvement from the baseline mean of 9.7 leaks/day–2.6/day after 6 months of treatment. Improvement was defined as a clinical effect with a greater than 50% reduction in symptoms. At 18 months, 84% of the patients were clinically improved, i.e. capable of eliminating heavy leaking episodes, 76% were capable of eliminating or reducing (by 50%) the number of daily used pads, and 47% were completely dry. In contrast, in the control group, the patients experienced either no improvement or a worsening of symptoms [16]. Similar results were reported in a randomized controlled trial with a significant decline in leakage episodes (improvement by 88%), pad use (improvement by 90%) compared with baseline, and with 56% of patients being completely dry [23]. Another prospective randomized multicenter study, with a 6 months follow-up, showed a significant reduction in the number of daily voids from 16.9 to 9.3 at with 56% of patients experiencing a reduction of 50% or more in the number of voids [5].

Many case series report the change in the average number of incontinence episodes from the baseline to 30 months post-implantation; the daily frequency of leaking episodes was significantly reduced from 10.9 to 4.2. Results from the Italian National Register showed a decrease in mean incontinence episodes from 5.4 to 1.2 in a follow-up of 12 months [19]. Similar results were obtained in a case series of 44 patients with a reduction in leaking episodes from 6.4 to 2.0 per day at 24 months; the reduction in pad consumption (mean reduction from 4.8 to 2.2 pads) was found to be statistically significant [23]. In a multicenter investigation, the number of pads used daily dropped significantly from 7.1 to 3.8 per day ($p < 0.0001$); thirty-three percent (33%) of the patients were dry and 28% experienced a greater than 50% decrease in pad use. At least 61% of the patients have experienced excellent or good results [5]. The bladder capacity and voided volume have been found on

urodynamic assessment to increase significantly compared to the baseline values. Voided volume has also been found to increase. The results seem to be maintained over time [10].

Results in neurogenic OAB

The first publications showed an improvement in bladder overactivity in patients with spinal cord lesions [20]. The treatment of refractory urge incontinence by chronic S3 nerve stimulation was feasible in selected multiple sclerosis (MS) patients. The fact that no irreversible changes to the bladder or nerves occur is an advantage of this treatment compared to destructive alternatives. However, the unpredictable evolution of the disease and particularly the cognitive decline can be a contraindication in cases of rapid progression of MS. In a case series, Chartier-Kastler et al. [7] reported 9 women with spinal diseases (including vascular myelitis, multiple sclerosis and traumatic spinal cord injury), who underwent neuromodulation. All patients reported an improvement of 75% in their visual analogue scale (mean follow-up 43 months). In another case series, Hohenfellner et al. [12] evaluated patients with neurogenic bladder (complete or incomplete spinal cord lesions, inflammatory neuronal reaction, borreliosis, lumbar herniated disk). Patients with incomplete spinal lesions seemed to be potentially suitable candidates and have an indication for the procedure, while those with complete or almost complete spinal lesions, seemed not likely to benefit from the procedure [12].

Complications of sacral nerve neuromodulation

Post-implant, the adverse events were associated with the devices or the use of stimulation. The most common problems were pain at the IGP or lead site, other type of pain, suspected lead migration, infection, transient electric shock, suspected device problem, adverse change in bowel function, persistent skin irritation, change in menstrual cycle, suspected nerve injury, technical problems with the device, and device rejection [21].

Conclusion

The technique of sacral neuromodulation is available for the treatment of neuro-urological conditions in which there is loss of regulation in the neurological systems that coordinate urinary storage and micturition. It is an effective treatment for the bladder overactivity, which is associated with polyuria, and hence, a decreased quality of life. When the pharmacological treatments have been tried to no avail, sacral neuromodulation remains an alternative to urological conventional surgical procedures in the bladder. It is important to distinguish the cases of neurogenic from those of idiopathic overactive bladder. It is essential to consider the psychological factors affecting each patient. The presence of urological pathology is a contra-indication for sacral neuromodulation. The major indication is bladder overactivity, followed by idiopathic chronic retention and chronic pelvic pain. Sacral neuromodulation is a minimally invasive technique but requires methodological rigor and a temporary percutaneous test. When good patient selection has been performed, more than three-quarters of the patients show a clinically significant improvement, but the results may vary according to each author's method of evaluation. The economic analysis reveals that the investment in the device pays off because it allows great savings compared to the cost of lower urinary tract dysfunction. Finally, this technique requires an attentive follow-up and adjustments to the electrical stimulation parameters in order to optimize the coordination between the neurological systems.

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Dorsal rhizotomy combined with anterior sacral root stimulation for neurogenic bladder

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Summary

A spinal cord lesion (traumatic or not) above the sacral micturition center may induce hyperreflexia of the detrusor, spasticity of the sphincter and vesico-sphincter dyssynergia. Eventually, alterations in the upper urinary tract can be associated with increased mortality in this patient population. Sacral rhizotomies combined with implantation of an anterior sacral root stimulator appear to be an effective method not only for the treatment of voiding dysfunction but also for defecation and sexual disorders. The clinical and electrophysiological checks and the surgical technique are described. In most series, the results show a constant improvement in the patient's functional status. Ninety percent of patients gain satisfactory continence and no longer require an incontinence appliance. Bladder capacity and compliance increase dramatically. As a consequence, urinary infection rate decreases. The majority of patients remain dry, and more than 80% have a complete voiding or a post-void residue of less than 50 ml and do not require any catheterization.

Anterior sacral root stimulation combined with sacral posterior rhizotomy is a valuable method to restore bladder function in spinal cord-injured patients suffering from hyperactive bladder.

Keywords: Neurogenic bladder; electric stimulation therapy; spinal cord injuries; spasticity; surgical procedures; rhizotomy; urinary tract infection; spinal nerve roots.

Introduction

The National Spinal Cord Injury Association [16] estimates that 250,000–400,000 individuals living in the USA suffer from a spinal cord lesion; the incidence of spinal cord lesion is 32 lesions per million inhabitants per year; this corresponds to 7,800 new cases per annum. According to this estimation, at least 330,000 people suffer from a spinal cord lesion (paraplegia or tetraplegia) in the European Union, and approximately 11,000 new cases are recorded each year. Twenty new cases per million inhabitants per annum represent the minimum incidence in Europe. Extrapolating the above statistics to the world population, gives an estimate of 32,000 people developing a spinal cord lesion each year. This represents more than 87 lesions per day, meaning a new lesion every 16 minutes. However, these figures are probably an underestimation, and apply to industrialized countries only. In all countries, the etiology is traumatic in nearly 80% of the cases, with a strong predominance of males; in half of the cases the spinal lesions are complete [6].

Complete lesions of the spinal cord are accompanied by a sensory-motor deficit, a major handicap for the patient, who cannot be cured in spite of research efforts in stem cells or nerve growth factors. Spasticity of spinal origin must be managed and an extensive examination must seek the underlying cause (syringomyelia, etc.). Occasionally specific treatment for spasticity may suffice (Baclofen® pump, DREZotomy, rhizotomy, etc.). Moreover, in 30–40% of the cases [7], neurogenic pain may create problems in the treatment of spinal cord-injured patients. The treatment of bladder disorders in spinal cord-injured patients must be integrated into the overall treatment plan. The ''spastic bladder'' is integrated in the nosologic framework outlined above, because it is among the principal complaints of patients presenting with a spinal lesion [7]. Neuro-urologic complications in the spinal cord-injured patient have, for a long time, represented the primary cause of mortality. The risk of deterioration of the upper urinary tract may occur at anytime in the life of these patients because of repeated urinary infections, vesico-ureteral reflux or hydronephrosis [22]. In suprasacral injuries, bladder dysfunction can be

dangerous to the upper urinary tract; the dysfunction is characterised by hyperactivity causing incontinence, and is often associated with vesico-sphincter dyssynergia causing incomplete voiding, and particularly high intra-vesical pressures causing reflux and dilation. A functional surgical procedure is currently proposed to the patient at risk, which preserves the anatomy of the urinary tract and restores the functions of this apparatus (bladder filling, and voluntary voiding).

Anatomy and physiology of the lower urinary tract

The lower urinary tract has two main functions: storage and periodic voiding of urine. These two functions are regulated by a complex neural control system involving a central pathway located in the spinal cord, pons and brain and peripheral autonomic and somatic neural pathways. This control system works like a switching circuit to maintain a reciprocal relationship between the bladder and outlet components of the lower urinary tract.

The storage (Fig. 1a) and periodic voiding of urine (Fig. 1b) are dependent on the reciprocal activity of two functional units in the lower urinary tract: a reservoir, the bladder and an outlet, i.e. the bladder neck and the smooth and striated sphincter muscles of the urethra. During urine storage, the bladder outlet is closed and the bladder smooth muscle is quiescent, allowing intravesical pressure to remain low over a wide range of bladder volumes. During voluntary voiding, the initial event is a relaxation of the pelvic floor and striated urethral muscles; this is followed by a detrusor muscle contraction and opening of the bladder neck. This activity is mediated by three sets of peripheral nerves: parasympathetic (pelvic), sympathetic (hypogastric) and somatic (pudendal) nerves. These nerves also contain afferent axons, terminating in the lower urinary tract, which are involved in initiating micturition.

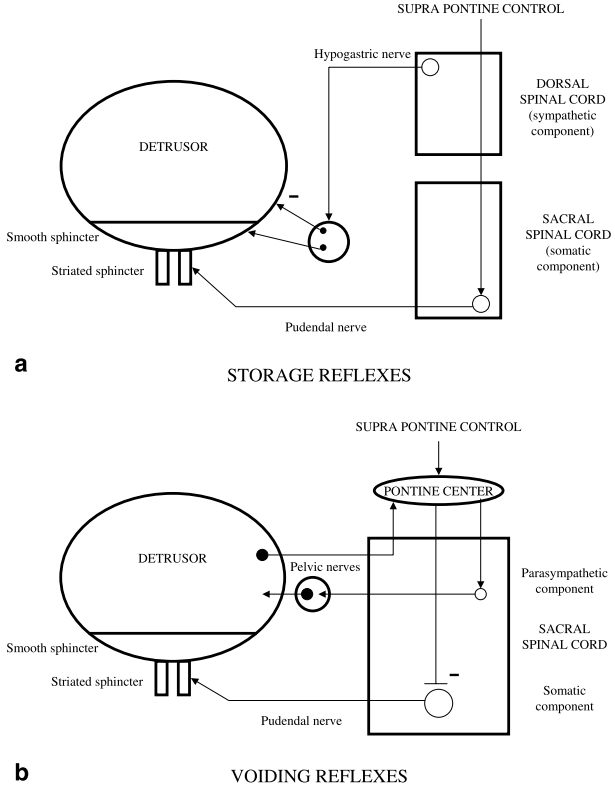

Fig. 1. Pathophysiology and neuronal network of vesico-sphincter functions Storage reflexes (a) and voiding reflexes (b)

Spinal levels

Efferent pathway

The parasympathetic efferent pathway is the main excitatory input to the bladder. Parasympathetic preganglionic axons originate in the intermediolateral column of the S2–S4 spinal cord and terminate in the postganglionic neurons in the bladder wall and in the pelvic plexus. The main neurotransmitter released by the parasympathetic postganglionic nerve terminals is acetylcholine. The sympathetic preganglionic neurons are located within the intermediolateral cell column of the T11–L2 spinal cord. They make synaptic connections with postganglionic neurons in the inferior mesenteric ganglionic neurons in the paravertebral ganglia and pelvic ganglia. Sympathetic postganglionic terminals release norepinephrine which acts on alpha-1 vesical and urethral receptors and beta-2 adrenergic detrusor receptors. The effect of norepinephrine on the former is a contraction of the bladder base and urethral smooth muscle. Norepinephrine, via an action of the beta 2 receptors, can also relax the bladder body.

Somatic efferent pathways that originate from the motoneurons in the Onuf nucleus of the anterior horn of the S2–S4 spinal cord innervate the external striated urethral sphincter muscle and the pelvic floor musculature. Somatic nerve terminals release acetylcholine, which acts on nicotinic receptors to induce a muscle contraction. The striated urethral sphincter also receives noradrenergic input from the sympathetic nerves. The combined activation of the sympathetic and somatic pathways elevates bladder outlet resistance and contributes to urinary continence. The striated sphincter (via the pudendal

nerve) is the unique element of voluntary continence and micturition.

Afferent pathway

Sensory information regarding bladder fullness is conveyed to the spinal cord via afferent axons in the pelvic and hypogastric nerves, which possess neuronal somata in the dorsal root ganglia at the S2–S4 and T11–L2 spinal segmental levels. Afferent fibers passing in the pelvic nerve carry impulses from tension receptors in the bladder wall to neurons in the dorsal horn of the spinal cord. These are mainly small myelinated (Aδ fibers) and unmyelinated (C fibers) axons [4]. In several mammalian species including human, the normal micturition reflex is mainly mediated by Aδ afferent fibers that respond to bladder distension. The C fibers, which have a high mechanical threshold, are usually unresponsive to bladder distension and are thus called silent C-fibers, but many of them do respond to chemical, noxious or cold stimuli.

Spinal centers

The sacral micturition center involves laminae VI, VII and X. The interneurons participate in local control of elementary programs via parasympathetic and somatic pathways [12]. The C fibers project to the dorsal horn and via a polysynaptic reflex with medullary interneurones form the ≪C reflex≫ of Bradley [4].

Pontine centers

Among the sub-encephalic centers involved in micturitional control, the most important are located in the pons. This part of the tegmentum receives afferent pathways from collateral spino-thalamic axons (from dorsal horn, laminae I and IV) to form the spino-pontospinal reflex or the ≪A reflex≫ of Bradley [4]. Two pontine centers have been characterized in mammals. The first is localized in the medial part of the dorsolateral pontine tegmentum, and is thus called the M-region or pontine micturitional center (PMC). The PMC projects to the sacral intermediolateral cell column, in which are located the parasympathetic center connected to the bladder motoneurons and the sacral intermedioventral cell column. The PMC is involved in the voiding phase via both these projections. The excitatory PMC projection to bladder motoneurons is responsible for an increase in bladder pressure during micturition. The relaxation of the striated urethral sphincter during micturition is due to excitatory projection to inhibitory interneurones in the spinal dorsal gray commissure.

The second pontine center, located more ventrally and more laterally than the PMC in the pontine tegmentum, is involved in the storage of urine during continence. During the storage phase, this L-center or pontine storage center (PSC) acts by direct excitatory projection to the urethral sphincter in the nucleus of Onuf [3].

Suprapontine controls

At the mesencephalic level, the periaqueductal gray (PAG) is considered as the main center involved in micturitional control. The PAG is thought to act as a central sensorimotor integrative relay of the micturition reflex, via the reception of sensory information concerning bladder fullness and the direct projection to the PMC. In the forebrain, the most documented structure is the pre-optic area of the hypothalamus, which is thought to play a role in the initiation of the voiding phase via direct projection to the PMC. In addition, the anterior cingulate gyrus, amygdala, red nucleus of the stria terminalis and septal nuclei are susceptible, when excited, to elicit bladder contraction. The superomedial part and the superolateral part of the precentral gyrus seem to be involved in voluntary control on the pelvic floor and in abdominal straining, respectively. Finally, the exact role of the cerebellum is not fully understood, but both afferent and efferent contributions to the micturitional reflex have been proposed.

Principles of the Brindley technique

Essentially, the technique consists of triggering a micturition by acute electrostimulation of the sacral roots. However, this acute stimulation depolarizes in a non-specific way, both the fibers within the pelvic nerves, which invest the detrusor muscle, and the fibers serving the urethral striated sphincter (contained in the pudendal nerves), resulting in a dyssynergic micturition. The effective micturition is obtained by exploiting the difference in relaxation time between striated and smooth muscle fibers. The striated fibers in the sphincter cease contracting immediately when the stimulation stops whilst the smooth fibers within the detrusor continue to contract as demanded. It is thus necessary to apply an intermittent stimulation [22]. The voiding of urine is thus obtained after several pulses of stimulation of 300 milliseconds with a frequency of 30 Hertz [6] (Fig. 2). The possibility of selectively stimulating parasympathetic

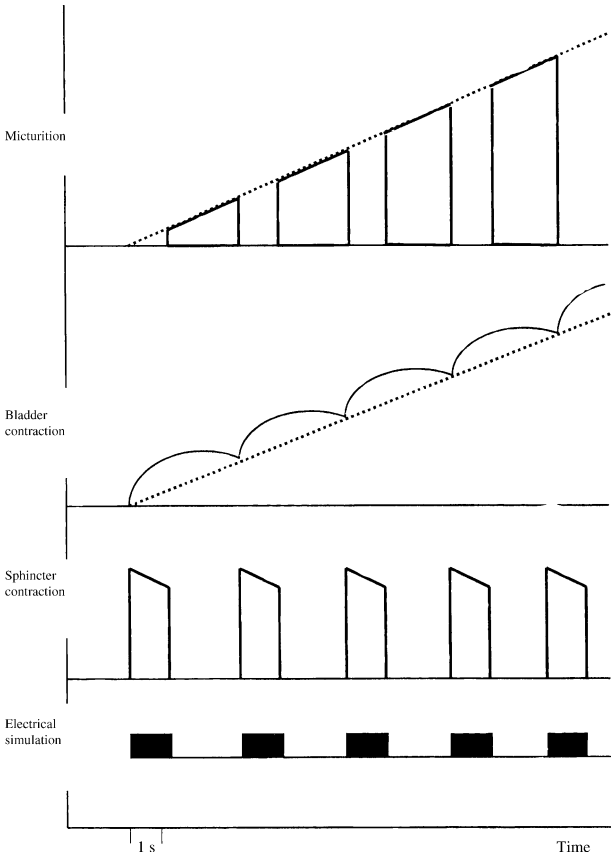

Fig. 2. The micturition by intermittent electrical stimulation is illustrated in this schematic representation. Micturition occurs during the gap at the end of each burst of impulses. The number of bursts delivered (approximately 4–10 to empty the bladder) varies according to the urinary volume, the degree of electrically induced detrusor-sphincter dyssynergia and the contracting ability of the detrusor

detrusor fibers is currently being researched. Others have described the possibility of blocking fibers investing the sphincter during stimulation. However, detrusor and sphincter hypereflexia prevent continence and do not allow complete and effective micturition [6]. It is thus imperative to perform deafferentation of the sacral center of micturition by performing rhizotomies of the posterior sacral roots and thus create a true sacral deafferented bladder. Thus, the spinal micturitional reflex is abolished, avoiding any resulting detrusor contraction through stimulation of its baroreceptors. In the same way, the striated urethral sphincter no longer contracts under the influence of the peripheral afferent pathways [5].

Indications

The technique is aimed at patients who are para- or complete tetraplegics, bearing a medullar lesion located over the sacral urinary centres. These patients present with a non-stabilised hyperactive bladder (central bladder) and have experienced, in the main, failure with re-education methods. The best indication is the patient presenting with uncontrolled leaks, on a non-disinhibited bladder, at weak capacity, and with or without vesico-sphincter dyssynergia [11]. Patients conserving a sensitive saving may perhaps benefit from the technique if they present bladder hyperactivity responsible for uncontrolled leaks, with chronic urinary retention being a source of severe infections and a threat to the upper urinary tract. The issues of assisting defecation and obtaining programmed erections in the male, are rarely held in prime consideration [5]. The technique, therefore, is directed to complete spinal cord injury sufferers presenting with a supra-sacral lesion. At present, this indication is met when a hyperactive bladder is the source of incontinence (associated or not with dyssynergia) and a risk to the upper tract, and this bladder hyperactivity cannot be corrected by traditional re-educative techniques (intermittent catheterizations and anticholinergics). The indications of Brindley technique can be described as follows:

- In paraplegic women not managed by the combination of self-catheterisations and anticholinergics.
- In tetraplegic women, the indication should be discussed with criteria the patient's dependence and third party interests. In low cervical lesions, self-catheterisation is often possible, but it is difficult and time-consuming, making the technique debatable. In middle cervical tetraplegias (C6), perineal self-catheterisation is not functional and not often considered; the choice should be made between the Brindley technique and continent cystostomy. Above C5, there are few alternatives apart from Bricker's non-continent diversion which requires collection pockets and human assistance 4 times a day (transfers, dressing) to assist urination (fewer complications and maintenance of body image). Finally, techniques of muscular-tendinous reanimation of the upper limbs can improve patients' quality of life (better handling of the stimulator).
- In paraplegic men, indications are found in the same conditions, but we must take into account the genito-sexual status (disappearance of reflex erections and reflex ejaculations). In fact, although in studies, more than 50% of spinal cord-lesioned patients have erections, they are mostly insufficient for penetration or last for a short time (unstable). Brindley technique is particularly indicated in paraplegic men without satisfactory reflex erection. Furthermore, after implantation, restoration of an erection remains possible by

having Brindley's specific programme, or intra-cavernous injections.
– In tetraplegic men, the Brindley technique should be put in the balance with the sphincterotomy and the choice should be made based on criteria of dependence and continence. The technique is also efficient in controlling autonomous hyperreflexia phenomena, and therefore, the existence of such phenomena will be determining the choice of treatment.

Material

The ''Finetech-Brindley Bladder controller system'' consists of an implantable receiver, which stimulates the sacral roots, and an external transmitter which is used to program the various parameters of stimulation. The implantable components consist of electrodes terminating in root traps, into which the appropriate sacral nerves are placed. The electrodes are connected by cables to a receiver-stimulator which is encased in silicone and implanted under the skin. The external material consists of an antenna connected to an external transmitter/controller device which allows programming of the stimulation parameters (frequency, duration, intensity), and provides the energy (by radio frequency coupling between antenna and receiver) for root stimulation (Fig. 3). For patient treatment, three different programs exist: I for micturition, II for defecation, and III for erection.

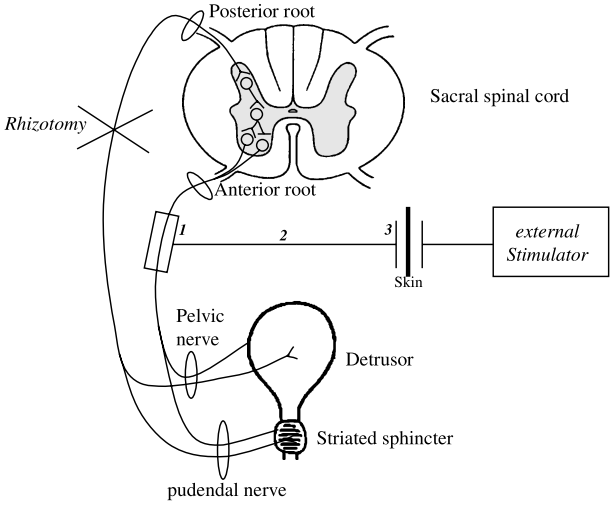

Fig. 3. Principle of the Brindley method. Electrical stimulation of the sacral anterior roots induces a ''voluntary'' and functional micturition. Posterior rhizotomies (S2–S4) suppress the vesicosphincter hyperreflexia, enhance continence and reduce dysautonomia symptoms. (*1*) electrodes, (*2*) cables, (*3*) a receiver-stimulator encased in silicone which is implanted under the skin

Surgical methods

The goal of Brindley technique is to realise a complete sacral deafferentation of the bladder and to connect sacral anterior roots with electrodes for electrical stimulation. Currently, we describe three methods (intradural, extradural, or sacral technique). The intradural method was introduced by Brindley in the seventies [5].

Intradural approach

Surgical intervention implies a lumbo-sacral stage of fixing the electrodes and a thoracic stage for implantation of the radio-receiver. The patient is operated on under general anaesthesia avoiding drugs that interfere with bladder contraction; curares and anticholinergics such as atropine would reduce the vesical responses to stimulation. The patient should be warmed to between 36 and 37 °C in order to avoid the influence of hypothermia on the autonomic nervous system. Hemodynamic monitoring (blood pressure, cardiac rate) is routinly performed. More recently, a specific, non-invasive marker of the autonomic nervous system (spectral analysis of the ECG) has been proposed for the early detection of reactional autonomous hyperreflexia. The patient is placed in ventral decubitus position with genupectoral support, in such a way as to leave free the perineal region and the lower limbs, for intraoperative monitoring. The horsetail roots are exposed intradurally, after a laminectomy

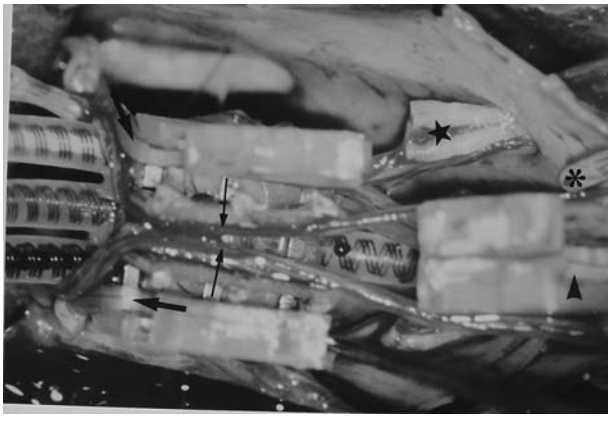

Fig. 4. Microphotograph of anterior roots placed into the 3-channel intradural implant slots. The 3-channel implant is composed of 2 electrode books. The upper book contains 3 parallel slots laterally for each (right or left) anterior S2 root and medially for both (right and left) anterior S3 roots. The lower book contains 1 slot for anterior S4 or S4–S5 roots. There are three electrodes in each slot (1 cathode in the centre and 2 anodes at the ends) to avoid stimulation of unwanted structures. Anterior roots of S2 (thick arrows); anterior roots of S3 (thin arrows); anterior roots of S4–S5 (arrowhead); right cut posterior root of S2 (star); right cut posterior root of S3 (asterisk)

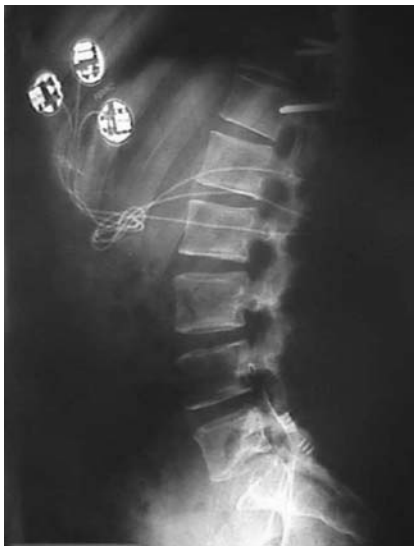

Fig. 5. Postoperative X-rays of an implanted patient. Note the osteosynthesis of the spine for T10 fracture responsible of paraplegia

reaching L3 and spreading along the sacrum roof (respecting the articular joints to avoid rachidian destabilisation). The stage of identification of roots is important, and is generally carried out with an operative microscope. Electrical stimulations are applied to the S2–S5 sacral roots to identify the motor and sensory parts and above all to identify by cystomanometric control which roots are involved in bladder function. Contraction of the buttocks and soleus muscle corresponds to level S2, that of the pelvic floor and of the big toe flexor to level S3 and that of the anal sphincter and of the perineum to level S4. The cystomanometric response is generally obtained by stimulation of S3, but sometimes of S4 and more rarely of S2. The S2 is sectioned along a length of 3 to 4 cm (or crushed). The motor roots are carefully freed from their arachnoid bridles and arranged in their respective stimulation compartment. Normally, the upper median compartment receives S3 while S2 is installed in the side compartments and S4 and S5 occupy the lower compartment. The dura mater should be air-tightly re-closed. The leads feeding the traps to roots run along a silicone mantle that ensures such air-tightness. The second thoracic stage can be carried out in the same ventral decubitus position (some prefer the lateral decubitus [2] or even dorsal decubitus [10]). The cutaneous incision is performed in accordance with the rib-cage. A small pocket is made for the radio-receiver which is fixed to the thoracic wall (Fig. 4). Connection of the three leads corresponding to the three pairs of roots is performed by subcutaneous tunnelling, after clinical and cystomanometric checking of the function of the device (Fig. 5). Total surgical time varies from 4 to 6 hours.

Extradural approach

The extradural method has been developed under the name of ≪Barcelona technique≫ [17]. Rhizotomy is performed first. After a dorsolumbar laminectomy, the sensory roots are sectioned where they emerge from the spinal cord. Opening the sacral canal allows placing the stimulation electrodes, extradurally, around each of the roots. The leads are connected to the subcutaneous radio-receiver. The extradural method does not require dissection of the roots in the intradural casing. These can be kept intact [22] in cases of contra-indication of the intradural method (infection, fibrosis, or presence of osteosynthesis material). This allows to have other options in the event of failure of the original approach.

Sacral approach

This technique, described recently by Robert *et al.* [13] may be called the ''Nantes technique''. It allows implantation in one procedure, and with only one posterior access. It combines the intradural method (rhizotomy and closure of the dural sac) and the extradural method (placement of the electrodes at the sacral root level). It also allows a shorter procedure time by carrying out rhizotomies, with precision, under the control of radicular stimulation, similarly to the intradural approach. Additionally, this approach limits the risk of root damage.

Results

Ninety percent (90%) of the patients describe that their quality of life improves significantly [10]. No series have reported deaths due to the technique [19]. The results for urinary reflex incontinence are consistent in the teams practicing complete rhizotomies; nearly 90% of the patients became continent [11]. This result is associated with a significant improvement in bladder compliance which may even return to normal. This is directly related to the precision and the number of rhizotomies performed. Thus, in the majority of patients, continence is definitively regained. The majority of patients void their bladder completely with a residual volume of less than 50 ml. These figures show the effectiveness of the stimulation device. This effectiveness remains stable in the long-term [24]. Of the patients, 80–100% had recurrent urinary infections preoperatively, sometimes life threatening. After implantation, 70% of the patients have sterile urine,

the others have nonfeverish transient leucobacteriouria which does not require specific treatment. The morbidity and mortality of infectious origin are greatly reduced among implanted patients. It is frequently noted that the vesico-ureteral reflux disappears, and urinary lithiases are reduced [22]. Renal function is constantly protected, provided that the stimulation parameters are correctly programmed. The Brindley technique does not cause deterioration of either the upper urinary tract or its function [20]. Autonomous hyperreflexia (AHR) is present among patients whose lesion is above the level of the sympathetic centers, and is associated with reflex release of catecholamines. Most series report reduction, or even disappearance of AHR. New cases of AHR have never been noted after surgery. These positive effects are due to the rhizotomies [22].

The erection stimulation program functions through stimulation of the S2 roots. Even if it is effective in 2/3 of the cases, in reality, it is only used by 1 patient out of 3 [6]. S4 root stimulation gives an improvement in the function of defecation by improving fecal transport into the rectum. Initially, the defecation stimulation program is regularly used by patients; however, usage later becomes occasional [6]. In addition, stimulation of S3 for micturitional use is sufficient to control the fecal function.

The spasticity of the lower limbs can be increased in the immediate postoperative period but this is always transient. It seems that, the hypertonia attacks become less severe. A reduction in the spasticity of the urethral striated sphincter is also observed. Sensory rhizotomy of L5 and S1 may be carried out during the implant procedure in patients presenting preoperatively with severe spasticity of the lower limbs, [10]. The Brindley system is not a contra-indication to the implantation of a Baclofen pump [22].

Impact on the quality of life

The Qualiveen scale [8] measures the specific impact of urinary problems on the quality of life of the spinal cord injured patient (IPSU) and explores 4 fields: embarrassment, constraints, fears in daily life, and a general index of the quality of life (QOL). This scale was validated on a reference population of 400 spinal cord-injured patients and thus serves to give reference scores. A recent study on the evaluation of the QOL using the Qualiveen scale has been undertaken among 37 patients subjected to the Brindley technique. In this study, the average score of IPSU was 0.84 in the Brindley technique group and 1.49 in the reference population, suggesting that the specific impact of urinary disorders on the QOL is smaller in the implanted population; in the same way, the median of the general index of QOL was 0.89 compared to 0.23 in the reference population, also suggesting a better QOL among implanted patients [23].

Economic consequences

Studies on the financial consequences of the Brindley technique showed a reduction in the annual costs per patient ranging from 3,000 to 8,000 dollars in the Netherlands [25] and from 8,000 to 14,000 dollars in the United States [9]. In the medium- to long-term, the Brindley technique is less expensive (after 8 and 5 years in the Netherlands and USA, respectively). However, the high variability of data and the differences in social security systems between countries show that this type of study must be carried out in each country concerned. The French ministry of health initiated a research program with the aim to measure the medico-economic impact of the Brindley technique on both its social security system and patient health. The results will be known in a few years.

Complications related to the technique

The CSF leakage risk is 2–3% [10]. One can observe a subcutaneous collection, sometimes up to the radio-receiver, but repeat surgery is rarely required. Maintenance of the decubitus position, prescription of Acetazolamide or of Glycerotone and delayed bladder stimulation (from one to several weeks) allow these effusions to disappear. Infection is a serious complication because it may require removal of the system and restoration of intermittent catheterizations. Its rate can reach 2.6% [24]. Meningitis is very rare. Contamination is caused sometimes through contiguity, mainly during surgery or hematogenically, manifesting itself several months after placing the implant. This risk should be evaluated as a potential indication for perioperative antibiotic prophylactic therapy. It is surprising that out of hundreds of implantations, no destabilisation of the spine was ever reported after placing a stimulator in patients with a deficient muscular structure. Only a pathological fracture in a patient with suspected osteomyelitis [9] and a non-significant aggravation of a pre-existent lumbar scoliosis were reported [21].

Lesions of anterior roots arise in 0–4% of cases [24]; they manifest themselves by the impossibility of obtaining effective bladder pressures through stimulation.

Intraoperative stimulation does not allow the prediction of these results that only appear later, between the 4th and the 7th post-operative day [21]. It is most often a neurapraxia that recovers within a period of 2–12 months. The intradural method theoretically exposes the patients to greater lesional risks [5].

Rhizotomies should involve all afferents from the bladder, i.e. bilaterally the posterior roots S2–S4, and for certain S5. They improve continence and protect the upper urinary tract by favouring low pressure refilling. Incomplete rhizotomies are commonly the result of a technical fault [1]. However, anatomical variations may exist [18] and contribute to the technique's inefficiency (variation of the number of levels regarding the bladder, localisation of the bladder afferents conveyed by the anterior roots, reflex activities contained in the underlying tracts). For eliminating a pronounced hyperactivity, anticholinergics can be used [9] but more often, it is necessary to perform additional rhizotomies. More rarely, the suggestion will be to divide or block either chemically or electrically the pudendal nerve. This nerve which innervates the striated sphincter, contains afferent fibers involved in segmentary reflexes. In men, rhizotomies lead to a complete loss of reflex erections and ejaculations which have great psychological importance. It is sometimes possible not to section the S2 posterior roots at the cost of a persistent hyperreflexia. The use of four or eight track implants allowing isolation of the intact posterior roots is possible during the time of stimulation of the motor roots [10]. The time needed for a failure to appear can vary from 1 month to 9 years [6]. About 7% of patients need repeat surgery [14], more often because of lead breaks, or faults in the receiver. The traps to the roots have never been questioned [1]. These deficiencies manifest themselves through intermittent dysfunctioning of the device. X-rays only rarely show a break of one of the leads, but the device can be replaced and the leads reconnected.

Conclusion

The Brindley technique is indicated in all para- or tetraplegic patients, presenting with a ''supra-sacral bladder'' resistant to the usual techniques of therapeutic re-education for incontinence, or in patients in whom the upper urinary tract is at risk because of the complications of neuropathic bladder. A multi-disciplinary medical team is required to implement the Brindley technique. The Brindley technique should be considered prior to any interventional urological procedure which aims to modify the anatomy of the lower urinary tract. In functional terms, the results are such that the future indications for Brindley technique should be expanded. Indeed, the technique involves the functional restoration of previously uncontrolled micturition, by electrically-induced controlled neural stimulation. Within this framework, the Brindley system can be proposed as an alternative not only to intermittent catheterizations, but also for the treatment of reflex micturition.

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Surgical therapy of neurogenic detrusor overactivity (hyperreflexia) in paraplegic patients by sacral deafferentation and implant driven micturition by sacral anterior root stimulation: methods, indications, results, complications, and future prospects

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Summary

Spinal cord injured patients with a suprasacral lesion usually develop a spastic bladder. The neurogenic detrusor overactivity (NDO) and the overactive external sphincter cause incontinence and threaten these patients with recurrent urinary tract infections (UTI), renal failure and autonomic dysreflexia. All of these severe disturbances may be well managed by sacral deafferentation (SDAF) and implantation of a sacral anterior root stimulator (SARS). Since September 1986 to December 2002, 464 paraplegic patients (220 females, 244 males) received a SDAF-SARS. The SDAF was done intradurally in almost all cases, which means that we used a single operation field to do a two-stages procedure (SDAF and SARS). The results include data on 440 patients with a mean follow-up of 8.6 years (18 months to 18 years) until December 2004. The complete deafferentation was successful in 95.2%. Of these patients, 420 paraplegics use the SARS for voiding, (frequency 4.7 per day) and 401 for defecation (frequency 4.7 per week). Continence was achieved in 364 patients (83%). UTIs decreased from 6.3 per year preoperatively to 1.2 per year postoperatively. Kidney function remained stable. Early complications were 6 CSF leaks and 5 implant infections. Late complications included receiver or cable failures and required surgical repair in 44 patients. A step-by-step program for trouble-shooting distinguishes implant failure from myogenic or neurogenic failure. SDAF is able to restore the reservoir function of urinary bladder and makes the patient achieve continence. Autonomic dysreflexia disappeared in most cases. By accurate adjustment of stimulation parameters, it is possible for the patient to have a low resistance micturition. The microsurgical technique requires intensive education. In addition, the therapist should be able to manage late complications.

Keywords: Sacral deafferentation (SDAF); paraplegia; sacral anterior root stimulation; SARS; detrusor overactivity; micturition.

Introduction

After a spinal cord injury that involves a complete suprasacral lesion almost inevitably neurogenic detrusor overactivity (NDO) develops, i.e. hyperreflexic, spastic bladder combined with an overactivity of the external sphincter i.e. detrusor-sphincter-dyssynergia (DSD). The conal parasympathetic and somatomotoric reflex-centres loose their coordination by the pontinomesencephalic centers of micturition and urine storage and also the voluntary control by the cortex is lost. NDO impairs the reservoir function of the bladder. DSD causes high resistance against micturition, which may only take place with increased pressure. Paraplegic patients suffer from reflex incontinence, recurrent urinary tract infections (UTI), autonomic dysreflexia (lesions above T6) and get threatened by renal failure. Conservative treatment frequently fails. In men, sphincterotomy is supposed to allow a reflex-voiding with low resistance but it can be associated with incontinence. Use of condom drainage is necessary. Nowadays, men quite often do not accept this management any more. Antimuscarinic therapy or the botulinum-A-toxin injection into the detrusor may successfully restore a sufficiently stable reservoir function but only in about 70% of the cases. The antimuscarinic therapy is very much limited by its side effects, and physicians frequently discontinue this therapy. Botulinum-A-toxin injection is well tolerated, but the big disadvantages include the high price and the need for repeated injections on average every 9 months. In spite of perfectly performed intermittend (self)-catheterisation or well done sphincterotomy in men, paraplegic patients continue suffering from incontinence, UTI, autonomic dysreflexia and finally renal failure. In such patients, the irreversible damage of the lower and upper urinary tract must be prevented. The surgical therapy includes sacral deafferentation (SDAF) and implantation of a sacral

anterior root stimulator (SARS); this method has been used very successfully since the middle 1980s.

Method

Historical development

In 1954, the first trials on electrostimulation in order to improve voiding function in neurogenic bladder dysfunction (NBD) were done. The electrodes were sewn onto the urinary bladder, but they migrated off the bladder wall, and this method was judged to be unsuitable [2, 3, 19, 31]. Electrostimulation of pelvic splanchnic nerves [14, 18] and the implants for sphincter stimulation [15] and a conus stimulator did not offer satisfactory results [24]. Brindley developed the implant and external device for anterior root stimulation (1969–1978), performed the first implantations in baboons and achieved the first implant driven micturition in 1971 [4]. Bursts of pulses and gaps between the bursts were used [2, 6]. The first implantation in human was done in 1976; the woman, suffering from multiple sclerosis, could not use the implant because the stimulation was painful. Incontinence and residual volume were just the same as with reflex micturition [6]. Brindley reported the first 50 cases after implantation of a sacral anterior root stimulator in 1986 and 1990 [11, 13]. The implant, the surgical technique and the outcome were described extensively. Anterior and posterior roots S2 and S3 were separated. Only occasionally and sometimes accidentally the posterior roots of S2 and S3 were cut or damaged. He reported improvement of bladder function with an increase of capacity and lower residual volume. Of the patients using the implant for voiding, 70% did not have any UTIs [11]. In 1986, Brindley decided to dissect the posterior roots S2–S5 routinely, strongly influenced by the work of Sauerwein in Bad Wildungen, Germany [25]. Sauerwein was convinced that a complete abolition of neurogenic overactivity could be achieved by the deafferentation of S2–S5. Sauerwein pointed out, "the spasticity of urinary bladder can destroy the bladder and kill kidney function". He was the first to separate S4 posterior and anterior roots and even S5 when necessary. The implantation of the SARS enables paraplegics to void voluntarily by means of an external transmitter (Fig. 1) [8, 13, 25, 26, 27]. Researchers in San Francisco used an extradural implant [1, 28, 32] but this approach to the posterior roots is more difficult, and, hence, continence could not be achieved as sufficiently as with the intradural approach.

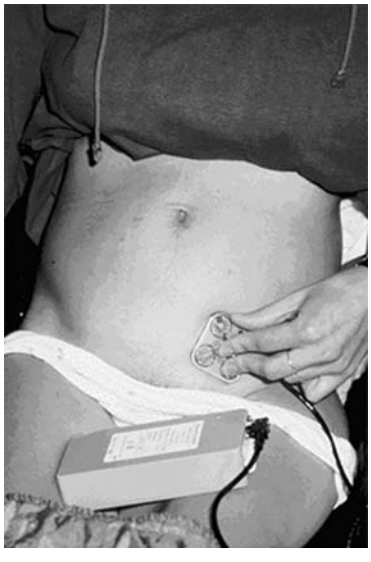

Fig. 1. Transcutaneous activation of the SARS implant

Benefits of SADF

The SDAF benefits can be described as follows [10]:

1) Safe continence in most patients following the complete abolition of neurogenic hyperactivity, provided that bladder neck function is intact.
2) Improvement of bladder capacity to normal and normalisation of compliance, provided that there is no serious fibrosis.
3) Prevention of deterioration of the upper urinary tract by diminution of dilatation, cessation of high pressure ureterorenal reflux and protection of kidney function.
4) Great decrease in the rate of UTI.
5) Reduction of active detrusor-sphincter-dyssynergia.
6) Abolition of autonomic dysreflexia triggered from bladder and bowel in most cases, although other mechanisms that may trigger autonomic dysreflexia may not be influenced.

Unavoidable deficits induced by SDAF

1. Abolition of reflex erection and reflex ejaculation (if these were present) following bilateral deafferentation S2–S5.
2. Great impairment or abolition of genital and perianal sensation (if they were present).

Certainly, meticulous neurological examination and patient's informed consent are mandatory in such difficult situations.

Effects of SARS

Urinary bladder

In order to do the surgical procedure properly it is quite important to know the different somatomotor and parasympathetic responses to stimulation. Somatomotor reactions will be found after stimulation with 1 V and pulse width of 100 μs. When stimulation of S4 roots is done the anal sphincter contracts and often the pelvic floor and the intrinsic rhabdosphincter do the same. The S3 roots activate the anal sphincter, the pelvic floor, the urethral intrinsic rhabdosphincter and usually the toe flexors. The S2 roots activate the gluteus medius, triceps surae, usually the pelvic floor and biceps femoris and often the anal sphincter. The necessary stimulation to activate the pelvic parasympathetic fibres may be stronger (5 V, 100 μs). In most cases, stimulation of S2 will not provoke contraction of the detrusor. S3 stimulation will cause the highest bladder pressure. S4 and sometimes S5

stimulation will also increase bladder pressure. Stimulating the posterior roots causes a rise in blood pressure, in quadriplegic patients [5]. Therefore, blood pressure should be usually lowered by nitroprussid-sodium during the procedure. One has to keep in mind that the somatomotoric activation will start at once, while the parasympathetic answer is postponed. This explains why paraplegic patients may void at low resistance after SARS although a degree of passive detrusor-sphincter-dyssynergia is still present [7].

Rectum, colon

In most cases, S3 and S4 SARS causes a rectal pressure rise. The rectum responds more slowly than the bladder. Longer bursts and longer gaps achieve cyclic variations in anal sphincter and rectal pressure [5]. Almost synchronously, maximal rectum pressure combined with minimal anal sphincter pressure develop. Thus many patients can defecate by such stimulation programs. Even when defecation does not take place, many patients experience a better transport of faeces from the pelvic colon into the rectum where manual evacuation may be necessary. Nevertheless, the stool evacuation becomes much quicker and easier. SARS may affect the function of the descending colon, too.

Sexual function

Stimulation of S2, and sometimes S3, may be used for inducing erection in men but not very effectively. SARS is not effective for ejaculation. In women, SARS of S2 may cause lubrification of the vagina.

Surgical procedure

The preparation for this surgical procedure must be meticulous. In order to minimize the infection risk, the skin must be in good condition and the patient should not have an UTI. Whole body disinfection is done 3 days prior to the operation. The patient is placed in prone position (Fig. 2). Pressure onto the abdomen should be avoided; otherwise, the surgeon may face heavy venous epidural bleeding. The operation starts with a laminectomy L4–S2 and the opening of the dura mater (Fig. 3). The deafferentation is done under microsurgical technique. Intraoperative urodynamic and arterial blood pressure monitoring allows to distinguish the dorsal and anterior roots by electrical stimulation with 10 V and 30 Hz. Electrical stimulation of the anterior root provokes a detrusor contraction and an accompanying somatomotoric reaction, i.e. plantar flexion and contraction of the anal sphincter (S3, S4) and contraction of gluteus medius muscle. When the lesion is higher than T6 the stimulation of the dorsal roots results to an increase of blood

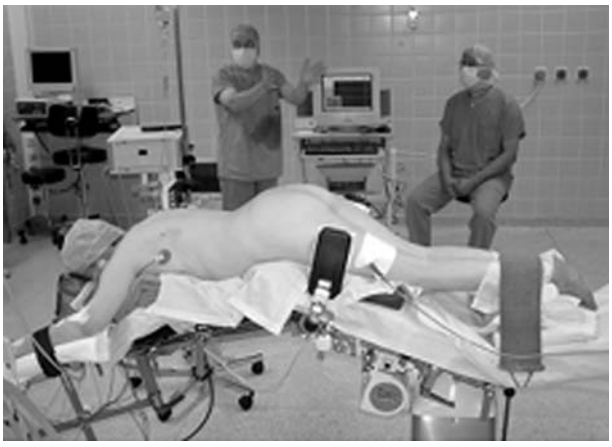

Fig. 2. Position of the patient for the SARS procedure

Fig. 3. Exposure of the roots intradurally

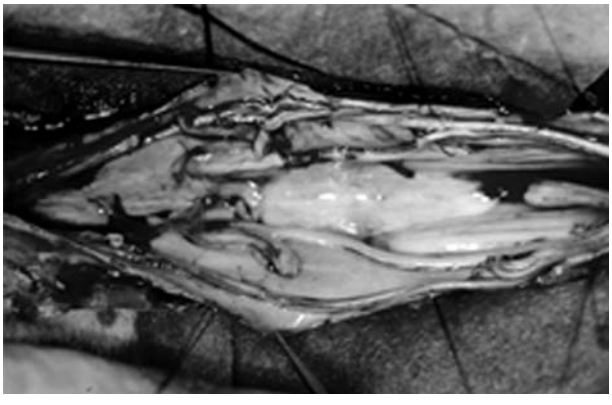

Fig. 4. Separation of anterior and posterior roots

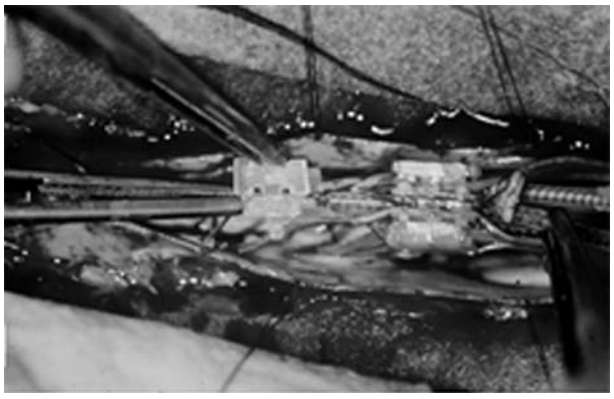

Fig. 5. Connection of the electrodes with the roots

pressure. After completion of SDAF, the implant is put into the spinal canal. The device has not changed since its development by Brindley [12, 13] (Fig. 4). S4 (S5) is put into the electrode's lower segment, the roots S3 are put into the middle part of the upper electrode segment, and the roots S2 are put into the upper segment of each side. The funnel is pulled over the cables down to the level of the dura. The dura is sewn water tight around the funnel. The correct function is confirmed by stimulation. The back is sutured and the cables are tunnelled to a reservoir at the flank. The patient then gets turned into the supine position and the receiver is connected to the cables and placed subcutaneously in the abdominal wall, according to the hand function and the preference of the patient. In the first two postoperative days, the patient is placed in reclining position with the head lowered in order to prevent headache and cerebrospinal fluid leakage. Within the first 7 postoperative days, an urodynamic evaluation is done, which confirms the successful complete SDAF, and the program of the external transmitter is set. Patients are now able to start micturition and defecation by SARS. The micturition by SARS is a

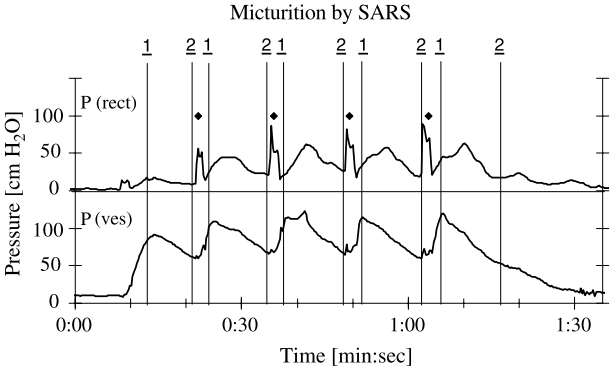

Fig. 6. Urodynamic evaluation of micturition by SARS

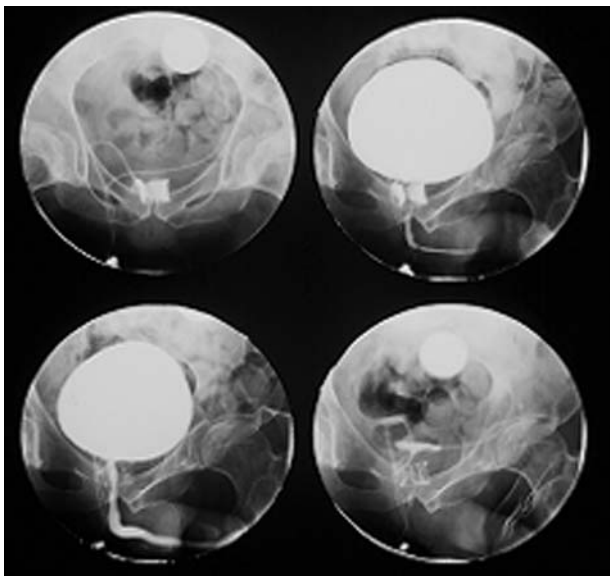

Fig. 7. Fluoroscopic documentation of urination by SARS

post-stimulus voiding (Fig. 6). Because of the quick relaxation of the striated muscles of the pelvic floor at the end of the stimulus, voiding takes place with low resistance (Fig. 7).

Indications

The indications for posterior rhizotomy and implantation of an anterior root stimulator are exclusively determined by bladder function. The requirements are described below [10]:

1. Motor and sensory complete spinal cord lesion; in cases of incomplete sensory lesion, the surgeon needs to be very experienced and a special informed consent should be taken concerning the loss of sensation in the segments S2–S5; paraplegia non-progressive or very slowly progressive.
2. Intact spinal reflex arcs S2–S4.
3. Intact detrusor function (no organic fixed fibrosis, no acontractility because of overdistention).
4. Security of a long-term therapeutic program for the spinal cord-injured patients and
5. A supportive family and social environment to such irreversible surgical treatment.

From a purely medical perspective, the indication clearly exists in cases with risk of renal failure and/or urinary incontinence, recurrent urinary tract infections, autonomic dysreflexia, failure of conservative bladder management, failure of therapy, and failure because of unacceptable side effects.

Patients

From September 1986 to December 2002, SDAF combined with SARS was done in 464 paraplegic patients, 220 females and 244 males. The main causes were paraplegia of traumatic origin (436), inflammation (12), neoplasm (12), and spina bifida (4). Quadriplegia was present in 190 cases and paraplegia in 274. About 75% of the patients had both motor and sensory complete lesion. Mean age was 33 years (14–67 years) at the time of the procedure. The duration of paraplegia was ranging from 0.5 to 46 years.

Results

Clinical und urodynamic findings (September 1986–December 2004)

Four hundred and forty (440) patients are still in a continuous follow-up with a current mean time of 8.6 years (18 months–18 years). SDAF was completely successful in 419 patients (95.2%) without any detrusor overactivity up to 500 ml and after provocative tests. In 8 patients, a second SDAF was done at the conus in order to achieve a complete cessation of NDO. In some patients, overactivity required a low dose of anticholinergic medication. The mean bladder capacity changed to 476 ml from 173 ml preoperatively. Some patients tolerate much higher volumes without getting incontinent, which is not desirable. Overdistention can reduce the effectiveness of SARS, and the patients can lose the ability to void by means of the anterior root stimulation. Continence was achieved in 364 patients (83%); in 22 patients, this required the additional implantation of an artificial sphincter. Four hundred and twenty (420) paraplegics are able to void voluntarily by SARS with a daily frequency of 4.7 micturitions. The stimulation parameters are shown in Table 1. Most other patients emptied the bladder by intermittent catheterisation and rarely by suprapubic bladder fistula. Four hundred and one (401) paraplegics are able to use SARS for facilitation of the defecation procedure with a frequency of 4.7 times per week. A retrospective study of 114 patients out of the first 120 patients operated in Bad Wildungen revealed that most of them experience a diminished use of laxatives and a dramatic decrease in the time they spent in the toilette (4.5 hours/week preoperatively compared to 2 hours/week postoperatively). UTI rate decreased from 6.3 per year preoperatively to 1.2 per year postoperatively. The kidney function did not deteriorate and remained stable at 66% of the mean normal value during the entire follow-up. The problem of autonomic dysreflexia with episodes of extremely high blood pressure disappeared in all cases with the exception of two; even in these patients the blood pressure rise was not as dangerous as before.

Table 1. *Stimulation parameters SARS*

Voltage	mean: 29 V (15–40 V)
Frequency	mean: 26/sec (15–40/sec)
Pulse width	mean: 400 µs (250–600 µs)
Burst	mean: 4 sec (3–6 sec)
Gap	mean: 12 sec (8–12 sec)

Complications

Early

Six cerebrospinal fluid leakages required a surgical revision with no further problems. Five infections of the implant (1%) required its removal. In 3 cases, it was possible to restore the function by reimplantation of an extradural device 6 months later and in one case 18 months later. Two wound dehiscences required a surgical revision and two haemorrhages did not require any intervention.

Late

The late complications were related to the implant. SARS failures may be due to defects of either the external transmitter, or the implant or to neurogenic or myogenic deterioration. Defects of the transmitter can be found by checking its function with a "flasher". All other failures require thorough analysis of micturition history and a video-urodynamic study. In addition, in order to diagnose neurogenic or myogenic damage, a transrectal electrostimulation (TES) with simultaneous cystometry is necessary. If one finds a normal bladder and somatomotoric response by TES, an implant failure is assured. If the patients can still use the implant for defecation and have a normal somatomotor response and no bladder reaction after TES one should suspect a myogenic damage of the bladder (overdistention) [20]. Complete lack of reactivity on sacral root stimulation S2–S4 means nerve damage. Eighty-one (81) implant defects were detected but not all of them resulted in loss of function. In 44 cases, implant repair surgery was necessary (change of the receiver 20, change of the receiver and cable-repair 6, cable-repair 6, extradural implantation 12). Any cable defect at a distance less than 5 cm from the entry point to the subarachnoid space (funnel) is difficult to mend and therefore, in such cases, an extradural implant is recommended [9]. In one case, a well functioning extradural implant (after repair) had to be removed because of infection. Myogenic damage after overdistention requires self-induced catheterisation (SIC) for weeks or

months; neurogenic failures do happen very rarely and require SIC indefinitely.

Discussion

According to the Finetech Company, about 2000 implantations of anterior root stimulators had been done all over the world till 2002. The original method is the intradural approach [25–27] but a few variations have been established. Clinicians in Barcelona and Singapore deafferentate at the conus medullaris [10]; in a second stage, the implant is put extradurally at the sacral roots after a laminectomy at the sacrum, if demanded by the patient. Otherwise, the patient does intermittent catheterisation. These patients do not have the benefits on bowel function. With SDAF at the conus the risk of damaging the anterior roots seems to be smaller [10]. Recently, a method of intradural SDAF and extradural implantation by a single sacral laminectomy was introduced in four patients with good micturition status afterwards [20]; one has to wait for further results. In the author's opinion, the advantage of the original method is the option of a second procedure for deafferentation in cases of insufficient SDAF and also a second chance for a new implant in cases of failure of the intradural implant.

The author's results [21] are in concordance with those in the literature. The method is recommended especially but not exclusively to quadriplegic women [23] and to quadriplegic men, who may not successfully be treated by conservative therapy. Sacral deafferentations and implantations have been reported in series which included from 6 to 96 patients by other groups [16, 17, 22, 30, 33, 34]. Continence rates between 83 and 91% have been reported, as well as significant decreases in UTI rate and an increase in bladder volume up to 565 ml [17]. Of these patients, 88% use the implant for micturition [17] and 55–66% for defecation [16, 17]. In the author's experience, the problem of autonomic dysreflexia and hypertensive crisis gets eliminated in most cases. This is in contrast to Schurch's results [29]; she found persisting autonomic dysreflexia while stimulating the bladder, although not as severe as preoperatively. Schurch postulated that stimulation of afferents that enter the spinal cord by the thoracic and lumbar roots and which are not influenced by sacral rhizotomy, could explain why autonomic hyperreflexia increases during urine flow [29]. The author described one young quadriplegic patient who had a SDAF performed in the beginning of 2005. He persisted in having autonomic dysreflexia by dermal provocation above S1 and while moving in the wheelchair. Brindley expects this to disappear within one year after surgery. Nevertheless, even patients who have a few episodes of blood pressure rises during SARS (4–6/day) they no longer have severe hypertension as they used to have during reflex micturition, with each UTI, space or during defecation.

Future prospects

One of the major criticisms is the need for posterior rhizotomy in order to abolish the NDO. Extensive research is done in order to find methods that could achieve a suppression of the posterior root function temporarily so the patients can have the advantages of deafferentation but men do not loose erection. At present, we do not have a sufficient substitute for deafferentation and there is no implant available, which could accomplish this.

Implant failures happen quite frequently. It is easy to change the receiver but cable repair is not easy and requires considerable operation time, about an hour for each cable. A plugging system at the funnel could make the repair safer and easier. A micro-electronic device without any cable could be an important development in the future. Research is done on this topic, but there is not still an implant like this available. One major problem in some patients is the difficulty in recognizing the amount of bladder filling and the associated risk of overdistention. In such a case, SARS fails and the patients have to do self-catheterisation. Miniaturised ultra sound devices are available, but they are still expensive and therefore, they are rarely recommended; there is a clear demand for a cheep device, which would be also easy to use.

Conclusions

SDAF interrupts the neurogenic detrusor overactivity of the urinary bladder in paraplegic patients. By means of a posterior rhizotomy S2–S5, a normal reservoir function is restored and the organ is preserved. SDAF-SARS must not be confounded with principles of neuromodulation. High percentages of these paraplegic patients regain safe urinary continence. Micturition is voluntary by an implant and an external transmitter. By means of an individualised accurate adjustment of the stimulation parameters it is possible to achieve a post-stimulus voiding and a low resistance micturition. The risk of high morbidity because of recurrent UTI, failure of kidney-function and autonomic dysreflexia gets eliminated. The microsurgical technique requires intensive education. The intradural approach offers a second chance for deafferentation in cases of incomplete first deafferentation and recurrence of hyperreflexia.

There is also a second chance for a new extradural implant in case the first implant must be repaired. In order to minimize implant complications, a highly efficient trouble-shooting system is mandatory. Restoration of implant-related dysfunction is possible in most cases. Implants with cable-plugs could make repair procedures easier. Development of microelectronic devices without cables could help in preventing implant-related complications. Nevertheless, the satisfaction of paraplegic patients with the outcome after SDAF and SARS is high because, undoubtedly, these procedures improve both the patients' level of independency and their quality of life.

Acknowledgement

This contribution is dedicated to Prof. Dr. med. Dieter Sauerwein, who was my medical teacher for 15 years. A few months before he had planned to retire he died after short serious illness in September 18th, 2004. Thanks are expressed to my colleague Dr. med. B. Domurath, who supported me in collecting the data.

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Sacral neuromodulation in the treatment of defecation disorders

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Summary

A large number of patients present with fecal incontinence due to idiopathic pelvic neuropathy or lesions of pelvic nerves, iatrogenic or secondary to other pelvic diseases or dysfunctions, involving sacral nerves. On the other hand, in many patients, constipation could be related to a peripheral neuropathy impairing normal defecation. Sacral neuromodulation (SNM) has been demonstrated as an effective approach in neuropathic defecation disorders. Its application is usually safe and easy, with a limited rate of complications or adverse events. The surgical procedure is made under local anesthesia. SNM effectiveness can be reliably tested during a short term period (up to 30 days) before the decision for a permanent implant. Results in most series show significant clinical improvement, with reduction in the number of incontinence episodes, decrease of incontinence score and improvement in patients' quality of life. A few reports suggest a potential and interesting application of SNM in constipation. Findings from anorectal manometry and other physiology examinations are not conclusive in order to define SNM mechanisms of actions and suggest that a multifactorial effect ''modulates'' the deficient neuromuscular system causing the defecation disorders.

Keywords: Neuromodulation; sacral root; stimulation; defecation disorder.

Introduction

Fecal incontinence

Fecal incontinence (FI) is the lack of control in evacuation of feces (liquid or solid) from the bowel. Estimated prevalence of this functional disorder ranges from 3.5% for women to 2.3% for men, with a rising percentage with age. However, the true incidence is likely to be higher due to the individual embarrassment to confess this problem and the social stigma related to it. FI is considered a distressing and socially incapacitating condition, with an enormous economic cost for patients and the society.

Traumatic sphincter lesions, idiopathic degeneration of the sphincter muscles, spinal injury or other neurological diseases have been considered the most frequent causes of FI in adults. Obstetric injuries are the most frequent cause of FI in women; 4–6% of women having a vaginal delivery will suffer from FI. Traditionally, treatment has been primarily conservative (diet, antidiarrheal drugs, rehabilitation and biofeedback). Many patients have been recommended to use absorbent pads and anal plugs only. In the past but also recently, different types of biomaterials have been injected in patients with internal anal sphincter dysfunction and secondary passive incontinence. Recent application of these bulking agents is under evaluation to determine long term results. Overlapping sphincteroplasty is performed for external anal sphincter defects. Although early results have shown improvement in 70–80% of patients, long-term efficacy seems to be significantly decreased with time. In cases with wide or multiple sphincter lesions, dynamic graciloplasty or artificial bowel sphincter implantation may be performed. The first option seems have a lesser incidence of long-term complications and a significantly higher therapeutic efficacy than the second one. Permanent stoma placement is another surgical option in extremely poor, intractable conditions or in patients who cannot be treated with the above-mentioned surgical procedures.

A large number of patients present with FI due to idiopathic pelvic neuropathy or lesions of pelvic nerves, iatrogenic or secondary to other pelvic diseases or dysfunctions. These clinical conditions could involve the neural supply of the anorectal region including both the somatic and autonomic (sympathetic and parasympathetic) nervous systems. Sacral nerves are the common site of these dual nerve supplies.

Electrical stimulation of sacral nerves has been thought to excite both nervous systems and thus ''modulate''

specific functions mediated by this complex nerve supply. Expected results of such a stimulation should be to give additional impulses not only to an inadequate pelvic floor musculature and pelvic organs but also to the sensitive pelvic fibers. This therapeutic approach is called sacral neuromodulation (SNM) or sacral nerve stimulation (SNS).

The first application of SNM was performed in 1906 in patients with micturition disorders. The first SNM implant in humans was performed in 1981 in patients with urinary urge incontinence and nonobstructive urinary retention. Over time a concomitant improvement in bowel symptoms was noted in some patients treated for urinary disorders. An increased anorectal junction angle and an increased anal canal resting pressure were documented and suggested to improve FI. As a result, SNM has been used to treat FI since 1995. Today, patient selection criteria in published reports [3, 11, 15–17, 28, 30, 34] remain widely heterogeneous. Initially, inclusion criteria were poor FI (at least one episode of either solid or liquid stool leakage per week) and failure of conservative treatment. Thereafter, functional defects of the striated pelvic musculature (without sphincter lesion) were the main criteria in the early studies [16]. Enrolled patients had decreased manometric squeeze pressure but normal pudendal nerve terminal motor latency (PNTML).

More recently, other, more precise indications have been investigated successively, including FI due to idiopathic sphincter degeneration [5, 28], iatrogenic internal sphincter damage [7], partial spinal cord injury [28], scleroderma [8], limited lesions of internal or external anal sphincters [13, 15–17], rectal prolapse repair [7] and low anterior resection of the rectum [18, 19, 26, 31]. Patient selection should take into consideration results of preliminary conservative treatment and features from physiology examinations (anorectal manometry, endoanal ultrasonography and anorectal electrophysiology). Incontinent patients without sphincters lesions with residual, even if reduced sphincteric or reflex function, should be candidates for the percutaneous nerve evaluation (PNE) test to evaluate the response to therapy; this is an optimal approach for patient selection to a permanent SNM implant.

Main contraindications to SNM are: sacral bony abnormalities, poor skin condition in the site of electrode placement, wide anal sphincter lesions, pregnancy, coagulation disorders, mental or psychological disturbances, presence of cardiac pacemaker or implantable defibrillator, immunosupression or high risk of infection, intractable inflammatory bowel disease and colorectal cancer. Many physicians consider previous pelvic irradiation as a contraindication to SNM; however, in patients with previous radiotherapy to the pelvis, FI could develop as a secondary effect of both irradiation and surgery. SNM application in these conditions seems to be effective [26].

Constipation

Prevalence of constipation is estimated to be ranging from 3 to 15% of the population; main symptoms are a reduced bowel frequency, abdominal pain, bloating, and difficulty in evacuation. Constipation could be differentiated into an organic and drug-related constipation and an idiopathic functional constipation (the most frequent type). In a number of patients, clinical symptoms are severe with a consequent impairment in quality of life.

Non surgical treatment is conventionally used as a primary therapy; it includes dietary and lifestyle advice, and, if necessary, drug therapy (laxatives, suppositories and enemas). When these are ineffective, rehabilitation is indicated and biofeedback should be used. However, some patients remain non-responders following conservative therapies. In these patients, subtotal colectomy with ileorectal anastomosis or stoma are the most frequently suggested surgical options. The first one could be associated with significant morbidity, while stoma with abdominal pain and bloating. SNM could be a valid surgical alternative in selected patients with constipation. Electrical stimulation should be able to ''modulate'' sacral nerves in order to recover specific functions for a correct defecation. Even if SNM is currently used in some centers for constipation, its value in this clinical condition is under evaluation.

Technique of sacral neuromodulation

SNM presents peculiar characteristics if compared with other surgical options for FI treatment. The first stage, the PNE test, is both a diagnostic procedure and a test of therapeutic efficacy. The second stage is the permanent implantation of the SNM system. Only if the PNE test produced good results in improving FI can a permanent implant be considered.

Peripheral nerve evaluation

The PNE test must be considered a fundamental phase of SNM therapy. It permits the implantation of an electrode adjacent to the sacral nerves in order to both eval-

uate their response to stimulation during the implantation procedure and the following period and also to assess the clinical efficacy on defecation disorders. Indeed, the PNE test, when brings about a significant improvement, it has a 100% predictive value [4, 9, 11, 13, 28] of positive response to permanent chronic stimulation. Traditionally, the electrode implanted for the PNE test is monopolar and used temporarily, limited to the test period. However, progress in the implantation technique has opened wider opportunities for performing the PNE test. Because electrostimulation of the sacral nerves elicits contractions of the striated pelvic floor muscles and a variety of sensations in the pelvis, the PNE test is preferably performed under local anesthesia. With the patient in the prone position (Fig. 1) and under sterile conditions, a few skin landmarks are identified bilaterally (Fig. 2) in order to facilitate the insertion of sheathed needles into S2, S3 or S4 foramina. S3 is the most preferrable because the sacral nerves are very close to the ventral side of this foramen. It is medial to the upper edge of the greater sciatic notch and a finger's breath from the sacral spine. Correct insertion into S3 foramen is confirmed by needle electrostimulation via a portable stimulator, which determines a ''bellows response'' (contraction and relaxation of the external anal sphincter and levator ani), and plantar flexion of the ipsilateral big toe; moreover, a sensory response is produced in the vagina/scrotum, perineum and perianal region. On the other hand, with stimulation through S2 foramen a contraction of the perineal muscles and external rotation of the leg can be seen while pulses through S4 foramen give a circular contraction of the external anal sphincter but no toe flexion. Position of the needle is checked by anteroposterior and/or laterolateral fluoroscopy views of the sacral area. When a good response is observed, an electrode is inserted and the needle gently removed. Electrode position is checked again by both electrostimulation and fluoroscopy. Thereafter, the electrode is secured on the skin by adhesive dressing and connected to the stimulator which is programmed (pulse width 210 μs; frequency 25 Hz; amplitude from 1 to 10 V) for a minimum 14-day test period. During this time, the patient collects a diary of normal bowel movements and micturition episodes, as well as episodes of fecal and urinary incontinence. In addition, a quality of life questionnaire can be completed and anorectal manometry performed. At the end of the test period, the temporary electrode is removed and the results are evaluated. If the clinical improvement concerns at least 50% of FI episodes, a permanent implant of the electrostimulator is planned. If the PNE test results are not clearly positive, a new PNE test could be programmed. If negative, a different approach should be investigated. The most frequent complication during the PNE test with a monopolar temporary electrode is lead dislodgement causing possibly a false negative result. Moreover, in a relevant number of patients showing good results during the PNE test, implantation of a definitive electrode provokes a different response, possibly due to a different position of the electrode in relationship to the sacral nerves. It could be reasonable to use the new model of definitive quadripolar electrode for the PNE test. As described below, the electrode can be implanted by a percutaneous technique under local anesthesia and connected to the external stimulator.

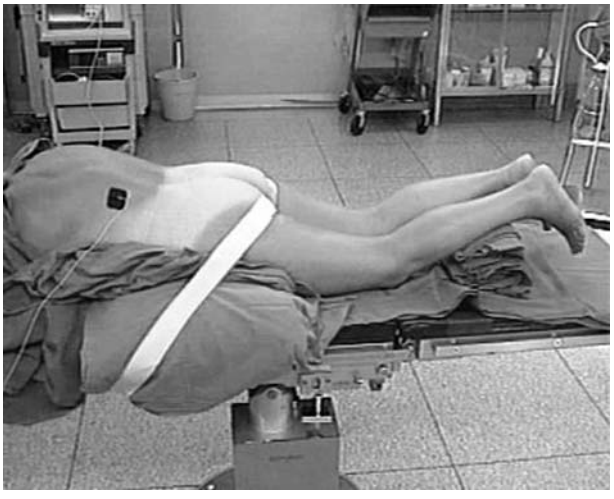

Fig. 1. Prone position required during application of the SNM device

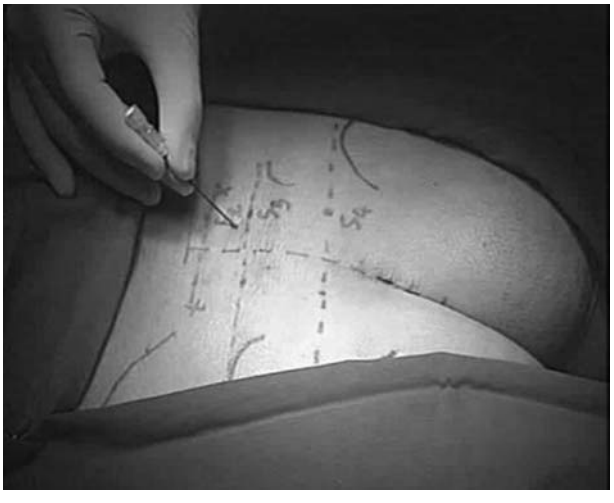

Fig. 2. Skin landmarks identified addressing the introduction of a needle during a SNM implant

With this lead the PNE test period can be longer for a more precise assessment of the response, changing more frequently the electrical field (trying different electrode combinations) and stimulation parameters. The electrode can be removed under local anesthesia in case of negative results; however, if the results are positive, implantation of the definitive stimulator only is necessary. In some cases, more than one temporary electrode can be placed for a wider stimulation involving the sacral nerves bilaterally. Consequently, bilateral implantation of the definitive electrodes could be indicated.

Permanent implant

Patients showing significant improvement following the PNE test are candidates for a permanent implant. The implant technique has been modified over time. The first implant procedure was performed under general anesthesia without curare in order to prevent striated muscle paralysis during stimulation. The sacral foramen chosen for the PNE test had to be found again by needle, repeating both electrostimulation and fluoroscopy in order to reproduce a response similar to the PNE test. Then, a long median incision (from 10 to 12 cm) of the sacral skin is required for insertion of the definitive electrode, which is directly inserted into the foramen and secured to the sacral periosteum. Changes in implant technique have been tried to simplify electrode insertion, first with minimal skin incision [23], then by a percutaneous insertion of a tiny lead [29]. Both these procedures do not need general anesthesia but are suitable for local anesthesia. This makes the procedure simpler and allows the surgeon to obtain the patient's cooperation in identifying appropriate responses. The ultimate model of electrode, the tiny lead (Fig. 3), is inserted using the Seldinger method and is fixed within the sacral foramen after removal of the introducer (Fig. 4). Electrostimulation and fluoroscopy are necessary to confirm correct electrode position. The electrode must be tunneled subcutaneously and connected to an extension electrode directed to the external stimulator when a two-stage implant has been planned or to the definitive stimulator in case of a single-stage implant. Also, the procedure for the stimulator insertion has been modified over time. Initially, it was implanted in a subcutaneous pocket into the anterior abdominal quadrant: it required a prolonged operative time including changing the patient's position. Successively, its placement in a pocket located in the gluteal area (Fig. 5) was suggested as a time-reducing method

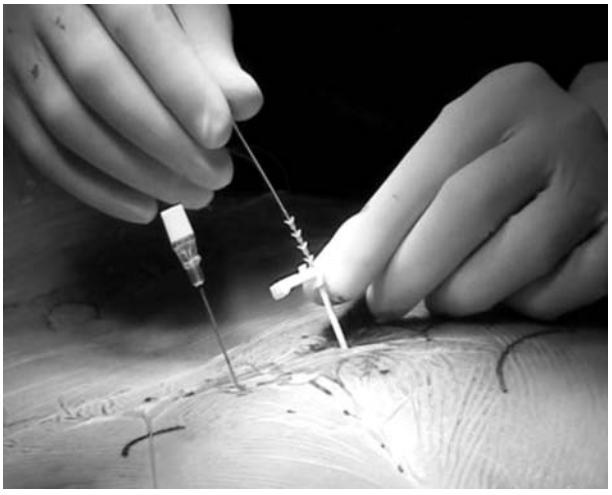

Fig. 4. Introduction of the tiny lead

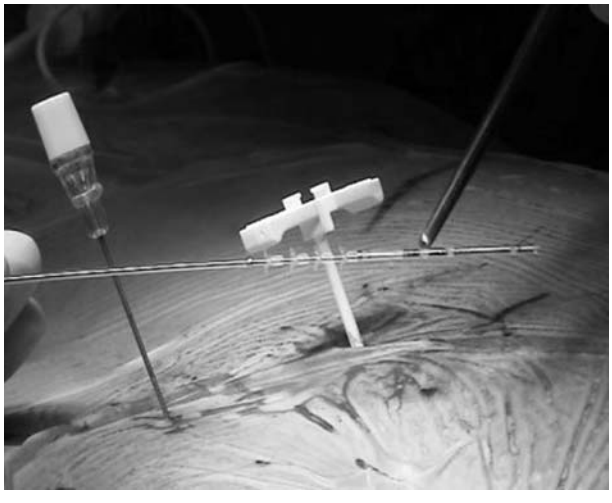

Fig. 3. The quadripolar tiny lead used for percutaneous implant

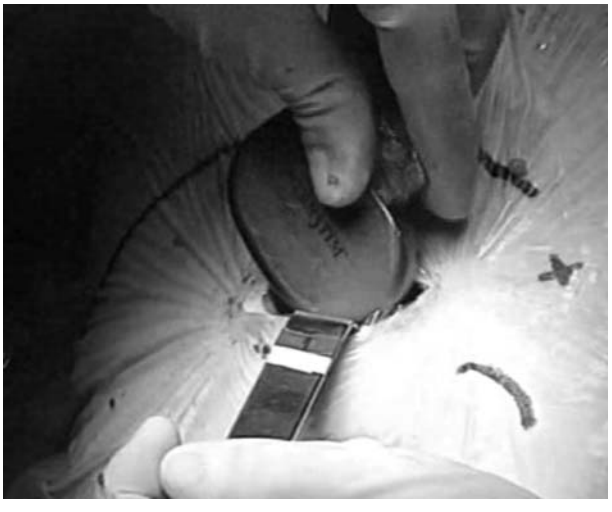

Fig. 5. Implant of the SNM electrostimulator into a subcutaneous pocket in the gluteal area

and as being more comfortable for the patient. Similar parameters used during the PNE test are selected for permanent stimulation, even though they may be changed in order to obtain the best response. Modification of the parameters is made using a telemetric programmer. The surgeon can use a programmer to modify all parameters of electrostimulation while the patient can use another model of programmer for modification of pulse amplitude (within a programmed range under physician control) or to switch off the stimulator when required. Battery life is related to the settings, with an estimated life ranging from 6 to 8 years.

Settings

Usually, the external stimulator is set at a frequency ranging between 10 and 25 Hz with a pulse width of 210 μs and an amplitude a little below or above the threshold for eliciting sensation. The most common sensations felt by the patient are a tingling or tapping in the buttock, anus, down the leg or in the vagina. The sensations could be different in location, type and intensity depending on which of the four electrodes is activated as anode or cathode. Preferred electrode polarity is determined by considering the lowest amplitude required to elicit patient sensations. The stimulator could be used as an anode, but with this configuration, pain at the stimulator implantation site is frequently noted by the patient. No significant adverse event has been reported following the stimulator implant. All complications were curable. In case of infection at the implant site, it is possible to remove the device and re-implant a new one after the infection has resolved.

Complications and adverse events

Complications of SNM are uncommon, ranging from 5 to 26% [1, 11, 28]. Only minor wound infection has been reported during the PNE test [11]. Rarely, the permanent SNM device needs to be explanted due to a complication (<5%). Pain at the electrostimulator site could be quite common in thinner patients. Wound infection is usually superficial, rarely being a cause of electrode removal (a later re-implantation could be planned). Electrode dislodgement after temporary implantation is quite frequent and has a significant impact on clinical interpretation of SNM efficacy. On the other hand, migration after permanent implantation is rare. In a review by Jarrett *et al.* [8], adverse events were documented in ten out of 266 (3.8%) patients receiving the PNE test (nine electrode dislodgement, one superficial skin infection). Adverse events were seen in 19 of 149 (12.8%) patients permanently implanted; three implant infections (requiring implant removal, one reimplanted); eight lead dislodgements (in seven patients, five reimplanted); six implant-related pains (treated with drug therapy) and one superficial wound dehiscence (spontaneous healing).

Results of SNM clinical application

Fecal incontinence

Evaluation of the clinical results of SNM has interest in order not only to assess, the therapeutic impact on FI but also to interpret the potential mechanisms of actions of SNM. In the early reports, the patient diary about the number of FI episodes was the main indicator of therapy effectiveness. Manometric measures have also been used to evaluate SNM effects on anorectal physiology. Moreover, a few score systems are used to measure severity of incontinence such as the Cleveland Clinic Incontinence Score and the patient quality of life or the Short-Form-36 (SF-36) or the Fecal Incontinence Quality of Life (FIQL) Index. Most reports concern patient series from single centers, but also multicenter studies and reviews are available.

Effects on patient symptoms

As showed in Table 1, all literature reports have documented a significant reduction of FI episodes in patients treated with SNM. In an European multicenter study [24],

Table 1. *Pre- and post-sacral neuromodulation (SNM) definitive implant results: episodes of incontinence*

Authors	Year of publication	Patients (no.)	Episodes of incontinence (no./week)		Pre vs. post variation
			Pre-implant	Post-implant	
Vaizey *et al.* [34]	1999	9	13.7	1.9	▼
Malouf *et al.* [15]	2000	5	18.2	1.4	▼
Ganio *et al.* [2]	2001	5	4.8	0	▼
Leroi *et al.* [13]	2001	6	3.2	0.5	▼
Rosen *et al.* [28]	2001	16	6.0	2.0	▼
Ganio *et al.* [3]	2001	16	5.5	0.3	▼
Kenefick *et al.* [9]	2002	15	11.0	0	▼
Matzel *et al.* [19]	2003	16	40.0	0	▼
Jarrett *et al.* [7]	2004	46	7.5	1.0	▼
Altomare *et al.* [1]	2004	14	14	0.5	▼
Uludag *et al.* [32]	2004	75	7.5	0.7	▼

▼ Decrease of post-implant vs. pre-implant value.

Table 2. *Pre- and post-sacral neuromodulation (SNM) definitive implant results: incontinence score*

Authors	Year of publication	Patients (no.)	Incontinence score*		Pre vs. post variation
			Pre-implant	Post-implant	
Malouf *et al.* [15]	2000	5	18.2	1.4	▼
Matzel *et al.* [19]	2003	16	40.0	0	▼
Rasmussen *et al.* [22]	2004	37	16	6.0	▼
Altomare *et al.* [1]	2004	14	15	5.5	▼
Ratto *et al.* [27]	2005	88	15.2	6.6	▼

* Cleveland Clinic fecal incontinence score, ▼ decrease of post-implant vs. pre-implant value.

evaluating the results following permanent implant in 34 incontinent patients (median follow up 23.9 months), the frequency of incontinence episodes fell from 16.4 ± 19.3 to 3.1 ± 5.5 at 12 months and 2.0 ± 3.3 at 24 months ($p < 0.0001$), with a statistically significant reduction of days with incontinence, with stain or with pads. Incontinence stopped completely in 37% of patients. A significant recovery of ability to postpone defecation and completely empty the bowel was also obtained under SNM. In our recent analysis, concerning rectal sensation in 16 patients permanently implanted, in all cases with constant or inconstant alteration before treatment, rectal discrimination was completely recovered following SNM. The feeling of complete evacuation was also recovered in almost all patients [25].

Measurement of FI scores significantly improved in all series, as reported in Table 2. In 88 patients definitively implanted with an SNM system and registered by the Italian Sacral Neuromodulation Group (GINS), the mean Cleveland Clinic incontinence score fell from 15.2 to 6.6 ($p < 0.0001$) [27].

Jarrett *et al.* [8] recently reported data from a literature review on SNM. Of 106 relevant reports, they selected only six patient series [5, 7, 13, 19, 28, 31] and a double-blind crossover study [22, 27] according to very strict criteria. A total of 266 patients included in the selected studies had a PNE test; 149 (56%) went on to permanent implantation, ranging from 26.7 to 80% in the single patient reports. Complete continence to solid and liquid feces was reported in 41–75% of untreated patients. After permanent implantation, 75–100% of patients experienced at least 50% improvement in the number of incontinence episodes. Also, significant improvements in the ability to defer defecation and Cleveland Clinic incontinence scores were reported.

Recently, Leroi *et al.* [14] reported results of the first double-blind multicenter study performed in France in 27 patients with definitive SNM implant for FI. The authors randomized blinded patients in a crossover protocol to stimulation ON or OFF for 1-month periods. The patients chose the preferred period of stimulation, which was continued for a final 3 months. Frequency of FI episodes was significantly lower during the ON than OFF period during both the crossover phase and final stage of the study and was associated with a significant improvement of the ability to postpone defecation, incontinence score, and anal sphincter function. These features indicate that the observed effectiveness of SNM is not due to a placebo effect.

Effects on patient quality of life

Sacral neuromodulation seems able to improve the patient's state of health and quality of life as reported by all studies (Table 3), although not always to a statistical significant degree. In a European multicenter study [20] assessing patient state of health with the SF-36 questionnaire, all domains (except for bodily pain) improved in the long-term follow-up when compared to baseline state. In particular, social functioning and mental health were constantly and significantly better 12 months after SNM implantation. In that study, all quality of life variables improved from baseline to the 12 months post-implant evaluation. In the GINS report [27], all SF36 parameters were significantly improved at the 12-months median follow-up after permanent SNM implant. Moreover, a statistical improvement was observed in physical,

Table 3. *Pre- and post-sacral neuromodulation (SNM) definitive implant results: impact on quality of life*

Authors	Year of publication	Patients (no.)	Scale	Results
Malouf *et al.* [15]	2000	5	SF-36	improvement of all parameters
Ganio *et al.* [3]	2001	16	SF-36	improvement of all parameters
Kenefick *et al.* [11]	2002	15	SF-36	improvement of social activities and physic health
Jarrett *et al.* [7]	2004	46	SF-36	improvement of general health, mental health, emotional role, social funtion, vitality
Altomare *et al.* [1]	2004	14	FIQL	improvement of all parameters
Ratto *et al.* [27]	2005	88	SF-36	improvement of all parameters except bodily pain

Table 4. *Pre- and post-sacral neuromodulation (SNM) definitive implant results: manometric maximum resting and squeeze pressures*

Authors	Year of publication	Patients (no.)	Pre-implant	Post-implant	Pre vs. post change
Maximum resting pressure (mmHg; mean)					
Vaizey *et al.* [34]	1999	9	40*	57*	▲
Malouf *et al.* [15]	2000	5	40*	49*	▲
Matzel *et al.* [17]	2001	6	63	65	≈
Ganio *et al.* [2]	2001	5	42	65	▲
Leroi *et al.* [13]	2001	6	77	61	▼
Rosen *et al.* [28]	2001	16	28	50	▲
Ganio *et al.* [3]	2001	16	38	49	▲
Kenefick *et al.* [11]	2002	15	35*	49*	▲
Matzel *et al.* [19]	2003	16	63	59	≈
Jarrett *et al.* [7]	2004	46	46*	49*	≈
Altomare *et al.* [1]	2004	14	36.5	32	≈
Uludag *et al.* [32]	2004	75	50	48	≈
Ratto *et al.* [27]	2005	88	60.5	71.9	≈
Maximum squeeze pressure (mmHg; mean)					
Matzel *et al.* [16]	1995	3	68	111	▲
Vaizey *et al.* [34]	1999	9	33*	75*	▲
Malouf *et al.* [15]	2000	5	80*	81*	▲
Matzel *et al.* [17]	2001	6	38	93	▲
Ganio *et al.* [2]	2001	5	67	82	▲
Leroi *et al.* [13]	2001	6	57	40	▼
Rosen *et al.* [28]	2001	16	59	120	▲
Ganio *et al.* [3]	2001	16	67	83	▲
Kenefick *et al.* [11]	2002	15	43*	69*	▲
Matzel *et al.* [19]	2003	16	69	97	≈
Jarrett *et al.* [7]	2004	46	63*	93*	▲
Altomare *et al.* [1]	2004	14	72	62	≈
Uludag *et al.* [32]	2004	75	83	82	≈
Ratto *et al.* [27]	2005	88	84.5	99.3	≈

* Values measured in cmH_2O, ▼ decrease of post-implant vs. pre-implant value, ▲ increase of post-implant vs. pre-implant value, ≈ similar post-implant vs. pre-implant values.

phychological and social functions evaluated with the Rockwood quality of life questionnaire. In a review by Jarrett *et al.* [8], patients' quality of life improved in the six series evaluated.

Effects on physiological parameters

Most studies report findings from anorectal manometry considered useful in order to interpret the mechanisms of SNM action. They are summarized in Tables 4 and 5. However, the effects of SNM on physiological parameters are not consistent and are often contrasting. Resting pressure increased after SNM in most series (Table 4); however, the reported increase was slight in comparison with preoperative data and rarely reached statistical significance [3, 11, 15, 21, 28, 34]. Also, according to some reports, squeeze pressure values increased (Table 4) when measured after SNM implantation but rarely the increase reached statistical significance when compared with pretreatment data [2, 3, 7, 11, 16, 17, 19, 28, 34]. In other series [2, 13, 15], either no change or decreased values were reported. Conflicting data have been reported concerning rectal sensation (Table 5). Vaizey *et al.* [34] reported results in nine treated patients. Mean post-implant rectal sensation levels increased in comparison with baseline values. However, Malouf *et al.* [15] found a decreased threshold level, no change in the urgency value, and an increased maximum tolerated volume in five patients after SNM compared with the pretreatment data. Leroi *et al.* [13], on six implanted patients, detected a decreased urgency and comparable mean values of maximum tolerated volume following SNM. Ganio *et al.* [2] reported a decrease in rectal sensation parameters after definitive SNM implant in five patients. In the multicenter GINS study [3], 16 patients were studied after definitive SNM implant. Both mean threshold and urgency values decreased when compared with pretreatment data (but only the difference in urgency was statistically significant). Kenefick *et al.* [11] reported a decreased mean threshold level after SNM in 15 patients. In a series of 16 patients, Matzel *et al.* [19] found a decreased mean threshold level, a similar mean urgency value, and an increased mean maximum tolerated volume. Jarrett *et al.* [7] reported, in a large series of 46 patients implanted at St. Mark's Hospital, a significant improvement of sensory function measured as threshold sensation, urgency sensation, and maximum tolerated volume. In a study on 15 patients, Uludag *et al.* [33] specifically investigated the effects of SNM on the rectum. Patients were submitted to barostat measurements of rectal sensation and compliance before and after a 3-week PNE test. In 14 of those patients, threshold sensation, urge sensation and maximum tolerated volume decreased significantly during stimulation. Median rectal wall tension decreased significantly related to all filling sensations while rectal compliance was similar before and during stimulation. These contrasting data are of no help in better understanding whether rectal sensation has a primary role in FI in patients treated with SNM, and, what the real effect of this therapy is on impaired rectal sensation. In a recent evaluation [24], we assumed that the conflicting results reported in other series reflected the obvious differences in pathogenesis causing FI in the treated patients. Indeed, there are incontinent patients with either hyposensitive or hypersensitive rectum while others present normal rectal sensation. Reevaluation after the definitive SNM implant led to inconsistent results. It is

Table 5. *Pre- and post-sacral neuromodulation (SNM) definitive implant results: assessment of rectal sensation*

Authors	Year of publication	Patients (no.)	Parameters	Rectal sensation (ml; mean)		Pre vs. post variation
				Pre-implant	Post-implant	
Vaizey *et al.* [34]	1999	9	threshold	45	145	▲
			urgency	73	173	▲
			max tol. vol.	95	175	▲
Malouf *et al.* [15]	2000	5	threshold	45	30	≈
			urgency	70	80	≈
			max tol. vol.	95	130	≈
Leroi *et al.* [13]	2001	6	urgency	175	124	▼
			max tol. vol.	203	200	≈
Ganio *et al.* [3]	2001	16	threshold	58.5	37	≈
			urgency	118.0	87.7	▼
Kenefick *et al.* [11]	2002	15	threshold	47	34	▼
Matzel *et al.* [19]	2003	16	threshold	40	25	≈
			urgency	60	70	≈
			max tol. vol.	150	200	▲
Jarrett *et al.* [7]	2004	46	threshold	41	27	▼
			urgency	92	71	▼
			max tol. vol.	129	107	▼
Altomare *et al.* [1]	2004	14	threshold	64	70	≈
			urgency	145	120	≈
			max tol. vol.	250	250	≈
Ratto *et al.* [27]	2005	88	threshold	54.3	46.5	≈
			urgency	119.9	97.9	≈

▼ Decrease of post-implant vs. pre-implant value, ▲ increase of post-implant vs. pre-implant value, ≈ similar post-implant vs. pre-implant values.

conceivable that SNM acts primarily by "modulating" the effects produced by the electrostimulation on the nerves. It has been postulated that there is a difference in the effect elicited on the initially hypersensitive or normosensitive rectum (expected to increase sensation levels) and that elicited on the primarily hyposensitive rectum (expected to decrease sensation levels). When evaluated in this light, the results of definitive SNM showed that the response of the majority of patients reflected this hypothetic mechanism, particularly as far as urgency and maximum tolerated volume are concerned (80% of patients). These patients had the best clinical improvement in FI as opposed to patients who showed variable effects of SNM on rectal sensation.

Constipation

Two patient series of permanent SNM implants have been reported [6, 10]. Ganio *et al.* [6] implanted 16 patients with defecation problems (digitation or straining), feelings of incomplete evacuation in more than 50% of bowel movements, and daily unsuccessful visits to the toilet and/or lack of normal sphincter behavior. All but one of these patients experienced a more than 50% reduction in defecation difficulty, in unsuccessful visits to the toilet and a significant improvement in the Cleveland Clinic constipation score (more than 80%). Kenefick *et al.* [10] reported 4 out of 10 patients who were definitively implanted with SNM, with a bowel frequency of two or fewer evacuations per week and straining for more than 25% of the time with either normal or slow gut transit. In 3 of 4 patients, a good clinical response was obtained, with improvement in the evacuations number per week, the Cleveland Clinic constipation score, and the percentage of time with the patient suffering from abdominal pain and bloating. The poor response obtained in the fourth patient was due to the electrode displacement during a car accident 1 week after implantation of the permanent stimulator. One of two patients with slow bowel transit in the Kenefick *et al.* [10] study had normal transit on follow-up. SF-36 quality of life scores improved in all eight subscales. Moreover, Kenefick *et al.* [12] reported a double-blind crossover study performed on two 36-year-old women with slow transit constipation; stimulation was set under the sensation threshold. When the electrostimulator was switched on, the evacuations number per week changed from 1 to 5 and from 2 to 4, respectively. Also, abdominal pain and bloating improved with increased frequency of defecation.

Mechanisms of action

SNM involves a variety of mechanisms of action and the knowledge of all of them remains incompletely

understood. However, some topics are well known. In most patients, the best response to SNM is obtained when the stimulation is given through the third sacral foramen because the largest amount of sacral nerves is adjacent to this foramen. In this site, the third sacral nerve root represents a mixed nerve including voluntary somatic, afferent sensory and efferent autonomic motor nerves (both sympathetic and parasympathetic). Possibly, the effects of SNM should be the result of stimulation on all these functions. In contrast to the physiologically rational and clinically relevant benefits shown by SNM, manometric features are not helpful in interpreting the mechanisms of action. In most series, both anal resting pressure and maximal squeeze pressure results do not change significantly in patients treated with an SNM device, and are not reliable parameters to predict therapy effectiveness. Interesting investigations would suggest a primary role played by rectal sensation in recovering continence to feces; so that, measurement of rectal sensation parameters could be of interest in monitoring the effects of SNM. Another significant effect of SNM could be produced on rectal motility, enhancing anal pressure slow-wave activity and decreasing the number of spontaneous anal relaxations; for such effects the integrity of the nervous peripheral-central connections is a fundamental prerequisite.

Discussion

Sacral neuromodulation can be considered as an effective therapeutic approach to treat patients suffering from FI which is associated with some kind of neuropathy as the primary or secondary cause. A large number of reports demonstrate the effectiveness of this therapy in improving the FI and patients' quality of life. In all series, episodes of FI are reported to decrease significantly and FI scores are improved. Urgency is frequently reduced, and altered rectal sensations, compared with those reported by patients preoperatively, are significantly ameliorated in most cases. Improvement of almost all variables measuring quality of life represents one of the most important results obtained by SNM in this group of patients who have severe psychological, social, and behavioral problems due to FI. However, the mechanisms of action of SNM are still not well understood. SNM seems to play a multiple role; it combines a variety of effects on anal sphincters, rectal sensation and motility via a modulated stimulation of different nerve pathways that are involved in defecation physiology, including afferent and efferent connections with the central nervous system. A better understanding of the action mechanisms will allow the assessment of which clinical conditions are appropriate candidates for SNM. However, the actual evaluation with clinical and instrumental assessment of FI, together with the PNE test give the best approach to selecting patients for a definitive SNM implant. In most cases, clinical results observed during the PNE test are reproducible, long-term durable, and not susceptible to the placebo effect. Early results of SNM for constipation are also encouraging, although preliminary, because they are obtained in patients who experienced a failure of medical and rehabilitative treatments. If effective, SNM can prevent major bowel resection or stoma. Correct indications are still debated, are under clinical evaluation, and range from evacuation difficulties to a decreased bowel frequency. In patients with both these clinical conditions there is some evidence of symptoms improvement by SNM.

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Sacral nerve stimulation for fecal disorders: evolution, current status, and future directions

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Summary

Sacral nerve stimulation (SNS) aims to recruit residual function of the anorectal continence organ by electrostimulation of its peripheral nerve supply. Since its first application for the treatment of fecal incontinence in 1994, its acceptance has been broadened and it is today considered a valuable addition to the therapeutic armentarium. Initially, its use was based on conceptual considerations, but changed to a pragmatic trial and error approach. Thus, the patients selection evolved: patients suffering from fecal incontinence due to a wide variety of causes are today selected for permanent SNS after a phase of temporary test stimulation. This test is highly predictive. If it is of clinical benefit, a neurostimulation device is implanted for chronic stimulation. Permanent stimulation not only improves or restores continence, but also has a substantial impact on quality of life. This has been uniformaly proven in multiple single and multicentre trials in a wide variety of aetiologies causing fecal incontinence. Despite the growing experience with the clinical use of SNS and its therapeutic effectiveness, the knowledge of its mechanism of action remains limited. Current research aims to improve our understanding of its action, to expand the spectrum of clinical applications and to implement recent technical developments.

Keywords: Neuromodulation; defecation; fecal disorder; sacral nerve stimulation.

Introduction

Fecal incontinence is a socially disabling problem that is underestimated but widespread. Approximately 2% of the general population suffers from the inability to control bowel emptying [34], and this rate rises with age: up to 11% of men and 26% of women over age 50 [39]. Its impact on society is substantial. With better diagnostic methods, the understanding of the physiology and pathophysiology of the components of the continence organ has improved in recent years. The maintenance of fecal continence is an integrated result of various organic functions:

1) the reservoir system of the rectum;
2) the outlet resistance of the sphincteric complex;
3) the sensory lining of the anal canal.

Their functional interaction is attained by a convergence of somatomotor, somatosensory, and autonomic innervation, mediated by fibers traveling with the sacral spinal nerves.

Evolution

The concept of recruiting residual function of an inadequate anorectal continence organ by electrostimulation of its peripheral nerve supply, i.e. the sacral spinal nerves, was adapted from the field of urology in the early 1990s. The rationale for applying sacral nerve stimulation (SNS) to fecal incontinence was based on both clinical observations and anatomic considerations. In the clinical setting, beneficial effects on bowel habits, anorectal continence, anorectal angulation and anal canal closure pressure were noted in urologic patients. From an anatomical standpoint, it was important to demonstrate, by dissection, the presence of a dual peripheral nerve supply to the striated pelvic floor muscles that govern these functions [24]. The sacral spinal nerve site is the most distal common location of this dual nerve supply. It was thought, therefore, that stimulating there could both enhance physiologic function [24] and improve the symptoms of fecal incontinence. Subsequently, in 1994, SNS was first applied for the treatment of fecal incontinence [25] in patients with deficits of the anal sphincter but no structural defect. Patients were selected after conservative treatment had failed, traditional surgical options such as sphincter repair were conceptually questionable, or the potential benefits of sphincter-replacement procedures (such as artificial bowel sphincter and dynamic graciloplasty, with their high morbidity) would not outweigh the risks in this population [2, 49].

As interest has increased in SNS for fecal incontinence, the technique has undergone continuous development, the patient selection process has been modified, and the spectrum of indications expanded. Today the treatment can be considered part of the armamentarium for treating fecal incontinence, despite the fact that our knowledge and understanding of its underlying mechanism of action is only slowly improving.

Patient selection and indications

Today, fecal incontinence from many causes can be treated with SNS. The current spectrum of applications reflects the evolution and expansion of the initial indication. Initially SNS was confined to patients with deficient function of the striated anal sphincter and levator ani, but with no structural defect [25]; residual function of the continence organ would be recruited by electrical stimulation. Thus, the initial patient selection for the SNS protocol was based on the clinical and physiologic finding of reduced or absent voluntary sphincteric function, but existing reflex activity, indicating an intact nerve-muscle connection; this was confirmed by intact anocutaneous reflex activity or by muscular response to pudendal stimulation with the St. Mark's electrode [32]. In this group of patients, the causes varied, covering a spectrum from postoperative sphincteric weakness consequent to anal and rectal procedures to total lack of voluntary sphincteric control as a sequela of cauda equine syndrome secondary to lumbar spine fracture. The latter suggested the potential efficacy of SNS in neurogenic incontinence [28] (Table 1). The common denominator of the heterogeneous etiologies addressed was reduced function and intact morphology.

This initial spectrum of indications and the positive clinical outcome were confirmed by single-center reports [6, 20] and, recently, in a prospective multicenter study [31] (Table 1). Clinical symptoms, measured as number of episodes with involuntary loss of stool, were significantly improved during permanent stimulation. Approximately, 90% of patients experienced a substantial (>50%) improvement, and 50% of patients gained full continence. In a recently published prospective multicenter trial, not only was the number of incontinent episodes or days with incontinence improved during the period of observation, but also the ability to postpone

Table 1. *Sacral nerve stimulation for fecal incontinence: clinical results*

Report	Patients	Pre-stimulation	Stimulation		Follow-up (months)
			Temporary	Permanent*	
Frequency of episodes of incontinence to solid or liquid stool over a 7-day period					
Initial concept					
Matzel *et al.* [32]	6	9 (2–19)	1.5 (1–5)	0 (0–1)	59 (5–70)
Leroi *et al.* [20]	6	2 (1–7)	0 (0–4)	0.5 (0–2)	6 (3–6)
Ganio *et al.* [6]	5	3 (2–14)	0	0	14 (5–37)
Ganio *et al.* [7]	16	5.5 (1–19)	–	0. (0–1)	10.5 (3–45)
Matzel *et al.* [31]	34	8.3 (1.7–78.7)	–	0.75 (0–25)	23.9 (1–36)
Modified concept					
Vaizey *et al.* [47]	9	8 (2–58)	0 (0–10)		
Malouf *et al.* [22]	5	*(see Cleveland Clinic Score)*			
Current concept					
Rosen *et al.* [41]	16	2 (1–5)	–	0.7 (0–5)	15 (3–26)
Kenefick *et al.* [16]	15	11 (2–30)	0 (0–7)	0 (0–4)	24 (3–80)
Ripetti *et al.* [38]	4	12†	–	2†,‡	24
Uludag *et al.* [46]	6	8.7 (2–38)	0.7 (0–10)	0.5 (0.5–0.7)‡	6.0†
Altomare *et al.* [1]	14	14 (11–14)§	–	0.5 (0–2)§	14 (6–48)
Jarrett *et al.* [11]	46	7.5 (1–78)	–	1 (0–39)	12 (1–72)
*Cleveland Clinic Continence Score***					
Malouf *et al.* [22]	5	16 (13–20)	–	2 (0–13)	16
Matzel *et al.* [30]	16	16 (12–19)	–	2 (0–7)	32.5 (3–99)
Rasmussen and Christiansen [36]	10	19.5 (14–20)	–	5.5 (0–20)	4.5 (1–12)
Altomare *et al.* [1]	14	15 (12.5–17.5)	–	5.7 (2–6)§	14 (6–48)

Data presented as median value, unless otherwise indicated
– Not available, * data at last follow-up, † mean value; SD and range not available, ‡ follow-up value: median of values at published follow-up intervals, § median values during a 2-week period, ** Cleveland Clinic Score [15]: 0: continent, 20: incontinent.

Table 2. *Permanent sacral nerve stimulation for fecal incontinence: clinical results – quality of life*

	Patients	SF 36			FIQL	
		Categories improved	Lifestyle	Coping/Behaviour	Depression/Self-perception	Embarrassment
Malouf *et al.* [22]	5	SF, RE, MH, RF	–	–	–	–
Rosen *et al.* [41]	16	–	increased*	increased*	increased*	increased*
Kenefick *et al.* [16]	15	all*except: HT	–	–	–	–
Ripetti *et al.* [38]	4	SF*, RE*, PF*	–	–	–	–
Matzel *et al.* [30]	16	–	increased*	increased*	increased*	increased*
Altomare *et al.* [1]	14	–	increased*	increased*	increased*	increased*
Matzel *et al.* [31]	34	SF*, MH, RE, RP, BP	increased*	increased*	increased*	increased*

SF 36: *RE* Role-emotional; *GH* general health; *MH* mental health; *BP* bodily pain; *RP* role-physical; *SF* social function; *V* Vitality; *HAT* health transition; *PF* physical functioning; *FIQL* fecal incontinence quality of life.
* Significant, – not available, [adapted from [32]].

defecation intentionally was significantly increased [31, 32, 45]. Recording of anorectal activity during temporary testing suggested that the effect of SNS was not limited to the striated sphincter muscle [47]. Subsequently, the indications for permanent SNS were expanded to patients suffering from fecal incontinence due to a deficiency of the smooth-muscle internal anal sphincter, to limited structural defects, and to functional deficits of the external and internal sphincter. Among these patients, (similarly to the initial group of patients) the causes varied widely and included scleroderma, degeneration or disruption of the internal anal sphincter (with or without concomitant external anal sphincter dysfunction), and idiopathic causes of sphincteric weakness. The symptomatic improvement in these patients was comparable to the initial group [16, 22] (Table 2).

During this initial work, it became apparent that the two-step selection of patients with two phases of diagnostic stimulation (temporary) was highly predictive of the therapeutic effect of permanent SNS [32, 45]. Consequently, patient selection was no longer based on a conceptual consideration of the potential mechanism of action, but on a more pragmatic approach. Test stimulation was indicated, not by an underlying physiologic condition, but by the existence of an anal sphincter and residual sphincteric or reflex function. Contraindications included pathologic conditions of the sacrum preventing adequate electrode placement (such as spina bifida), skin disease at the area of implantation, anal sphincter damage amenable to direct repair or requiring a sphincter substitute (e.g. artificial bowel sphincter, dynamic graciloplasty), trauma sequelae with micturition disorders or low bladder capacity, pregnancy, coagulation deficits, psychological instability, low mental capacity, and presence of a cardiac pacemaker or implantable defibrillator. This pragmatic, trial-and-error, patient selection process resulted in numerous published series [32, 45]. Most studies have presented patients with very heterogeneous pathophysiologic conditions, outlining the range of patients who might benefit from SNS. In only one study a rather defined patient population is described: 75% of the participants suffered from fecal incontinence of neurogenic origin [41].

Most commonly, the clinical outcome is reported as an improvement in: a) incontinent episodes or days with incontinence during the period of observation, and b) quality of life. The studies may vary with regard to design and number of patients, but there is general agreement regarding the two-steps stimulation in patient selection for permanent implant. The short- and long-

Table 3. *Permanent sacral spinal nerve stimulation for fecal incontinence: anorectal physiologic findings*

		Resting pressure	Squeeze pressure	Threshold volume	Urge volume	Maximal tolerablevolume
Matzel *et al.* [25]	3	ø	increased*	ø	ø	ø
Malouf *et al.* [22]	5	ø	no consistent change	ø	ø	Increased
Ganio *et al.* [7]	16	increased	increased	decreased	decreased	–
Leroi *et al.* [20]	6	ø	no consistent change	–	–	decreased
Rosen *et al.* [41]	16	increased*	increased*	decreased	decreased	no effect
Kenefick *et al.* [16]	15	ø	increased*	decreased*	ø	decreased
Ripetti *et al.* [38]	4	increased	increased	decreased	ø	–
Matzel *et al.* [30]	16	ø	increased *	decreased	ø	increased
Altomare *et al.* [1]	14	ø	ø	ø	decreased	ø

* Significant, ø no effect, – not available, [adapted from [32]].

term effects of SNS have been demonstrated in multiple single and multicenter trials (Table 3). The favorable clinical outcome data (Table 3) confirm this pragmatic selection process.

Test stimulation

Because no other predictors of SNS outcome exist at present, patients are uniformaly selected for operative implantation of a permanent neurostimulation device on the basis of clinical improvement during test stimulation (documented with standardized questionnaires and diaries). The testing procedure is considered effective if the frequency of episodes of fecal incontinence (documented by bowel-habit diary) is alleviated by at least 50% and the improvement is reversible after discontinuation. The method of choice for permanent stimulation is the unilateral implantation of a foramen electrode on the spinal nerve site demonstrated to be therapeutically effective during test stimulation. Bilateral foramen electrodes can be considered if unilateral stimulation is insufficient and bilateral test stimulation provides acceptable results [29].

Technical evolution

The technique has been described extensively [9]. In short, after successful stimulation with needle electrodes placed at the target nerve/s through the sacral foramen, electrodes are placed temporarily to test the clinical benefit of low frequency. Two technical options are used for subchronic percutaneous nerve evaluation (PNE): a temporary, percutaneously placed, lead (or multiple leads) (Medtronic 041830) that will be removed at the end of this phase, or operative placement of a quadripolar lead, ''foramen electrode'' (Medtronic Model 3886). Recently, a less invasive technique that uses a foramen electrode with a modified anchoring device, the so-called ''tined lead'' placed through a trochar (Medtronic Modell 3550-18), has been proposed and is increasingly used [43]. Both types of leads are connected to an external pulse generator for screening (Medtronic Screener 3625, Medtronic, Minnesota), with a percutaneous extension cable. Percutaneous placement of temporary test stimulation leads can be done on one or multiple spinal nerves to offer the option of testing the effect of stimulation of different sides and levels or of synchronous stimulation of multiple nerves in an awake patient [44]. The placement of the foramen electrode or ''tined lead'' is usually limited to one site. At the end of the screening phase, the percutaneously placed temporary test stimulation lead is removed and, if successful, a permanent system consisting of an electrode, connecting cable and pulse generator is implanted. The operatively placed foramen electrode is either removed (if unsuccessful) or connected to an implanted pulse generator (''two-stage implant'' [10] if successful), offering the advantage of identical positioning of the electrode during screening and therapeutic stimulation. Bilateral placement of foramen electrodes (if performed), is based either on improved outcome of bilateral stimulation during the screening phase [29] or on conceptual considerations [37]. The stimulation parameters are those of SNS in urology, sometimes with slight modifications. The combination most effective (with regard to required voltage and the patient's perception of muscle contraction in the perineum and anal sphincter) is commonly chosen for permanent stimulation: pulse width, 210 μsec; frequency, 15 Hz; on–off: 5–1 sec or continuous stimulation. The level of stimulation is usually adapted to be above the individual patient's perception of muscular contraction or perianal sensation and is adjusted if necessary.

Outcome

As noted above, in most studies quantitative measures are used to describe the clinical benefit, such as days with incontinent episodes/period of observation, absolute numbers of incontinent episodes/period of observation, ability to postpone defecation (in minutes), and percentage of improvement. Even though published reports differ with regard to patient population, a general pattern of outcome can be observed (Table 1); the results of the screening phase are reproduced with the permanent implant. When compared with baseline status, the clinical improvement is highly significant. The rate of complications is relatively low [32, 45]. These include pain at the site of the electrode or pulse generator, electrode dislodgement or breakage, infection, loss of effect, or deterioration in bowel symptoms. In only 5% of the patients, discontinuation of treatment and device removal has been necessary because of loss of effect, deterioration of symptoms, pain, lead dislocation, or infection. When infection has necessitated removal, re-implanation at a later date has been successful [22]. Outcome assessment has evolved. Initially, the usual measures were the number of incontinent episodes or days with incontinence during a set observation period (based on bowel-habit diary). Subsequently, aspects of quality of life were added to the evaluation (Cleveland Clinic Continence Scoring System [14], SF36 [48] and

FIQL Score [40]). The therapeutic impact of SNS is most evident when disease-specific quality-of-life instruments are applied. The disease-specific FIQL showed highly significant improvement in all four categories (lifestyle, coping/behavior, depression/self-perception, embarrassment) in both single-center and multicenter studies (Table 2) [32, 45].

Anorectal physiology

Numerous efforts have been made to correlate the clinical outcome of SNS with results of anorectal physiology studies, but the effect of chronic stimulation varies greatly among published reports (Table 3) [32, 45]. The data are in part contradictory and inconclusive and sometimes unreproducible. The most common finding was an increase in striated muscle function, expressed as improved squeeze pressure. In one study, the duration of voluntary contraction was shown to be increased [20]. The effect on resting pressure and rectal perception is inconsistent, although a trend toward decreased sensory and urge thresholds is apparent. Hyposensitivity of the rectum improved during chronic stimulation [42].

Rectal manometry (24-hr) has indicated that the effect of SNS is not limited to sphincteric function and rectal perception. Reduction of spontaneous rectal motility [46, 47] and spontaneous anal sphincter relaxation [20] are qualitative changes in anal and rectal motility. Changes in blood flow recorded by rectal doppler flowmetry during stimulation give further indication that SNS affects autonomic function of the distal bowel [18]. Improvement in anal sensory function and sensibility of the perianal and perineal skin during SNS has been reported in one study [41]. Recently, it has been demonstrated that the physiologic changes induced by SNS can be observed not only on the target organ, but also in the central nervous system [3, 21].

Thus, the clinical effect of SNS is likely multifactorial, based on multiple physiologic functions. The understanding of the relative importance of each of these functions and their dependence on pathophysiologic preconditions is unclear. It may simply be that SNS works differently in different patients. The number of studies with a homogenous patient population is limited, and most studies represent a heterogeneous aggregation of patients with a wide variety of underlying pathophysiologic conditions; thus, any firm conclusion regarding the underlying mechanism of action is unreasonable. A potential placebo effect is unlikely. The long-term benefit has been shown to be sustainable; patients who experienced clinical deterioration had their therapeutic benefit restored after technical problems with the neurostimulator (of which they were not aware) were corrected. The clinical effect has been also confirmed in a double-blind crossover trial [17].

Future directions

The future direction of SNS in the anorectal dysfunction is in part outlined by current research. Various interrelated clinical and technical issues are addressed by ongoing research aiming to increase our knowledge of the appropriate use of SNS and its mechanism of action. A broad spectrum of patients is today successfully selected by the current pragmatic approach. Some small case series and individual case reports have investigated the effect of SNS in groups of patients presenting with distinct conditions and well defined anorectal physiology findings, e.g. muscular dystrophy [4], rectal resection and adjuvant chemoradiation [37], sphincteric gap requiring surgical repair [5], neurologic dysfunction [12], rectal prolapse repair [13], and rectal resection for cancer [14, 29]. Initial results are promising, but need to be confirmed in large prospective trials. This approach hopes to pinpoint clinical predictors of responders, potentially obviating test stimulation; also, the focus on distinct pathophysiologic conditions may be helpful to our understanding of how SNS works.

By applying SNS to patients with sphincteric dysfunction [5] in whom surgical repair is planned, and thus potentially avoided, the current treatment algorithm for fecal incontinence is challenged. This has special interest, because we have learned in recent years that the short-term benefit of sphincteric repair deteriorates over time; indeed, after 5 years it has been shown to be less favorable [8, 23]. However, data of the long-term efficacy and durability of SNS are variable. A multinational registry could be helpful for both long-term follow-up and subgroup analysis. Not only are surgical treatment options are challenged by SNS, but also the role of SNS in the treatment algorithm needs to be reconsidered. It is currently viewed as an option if conservative therapy has failed. However, because test stimulation is a highly predictive diagnostic procedure with very limited morbidity, it is used today much more liberally to explore potential future patient groups. It will be worthwhile to compare the very early use of SNS in the treatment algorithm with the results of conservative treatment. Electrostimulation of the sacral nerve depends on the appropriate placement of the electrode to the target nerve,

and anatomic pathophysiology may hinders this. This problem could be overcome with stimulation at the level of the pudendal nerve with a minimally invasive microstimulator [33]. Although further research is required to prove the efficacy and reliability of pudendal stimulation for anorectal dysfunction, recent work indicates that even more peripheral stimulation, i.e. tibial, may be beneficial [35]. To increase its efficacy, SNS has been applied bilaterally in only a few patients. It remains to be determined whether bilateral stimulation leads to an improved and more durable clinical response; the observed increased effectiveness of bilateral SNS or of unilateral stimulation of more than one nerve may depend on the individual innervation pattern of the patient [26]. The validity, accuracy, and reproducibility of electrophysiologic testing (whether during treatment to monitor functional changes or during the initial operation to optimize electrode placement), must continue to be investigated.

It is also noteworthy that the stimulation parameters, especially subsensory threshold stimulation, are also under investigation. Not only variations may increase efficacy (by prolonging battery life) but may provide insight into the clinical effect of SNS; this in some patients may not be dependent on the perception of stimulation [19]. The two-step test stimulation process is of pivotal importance in patient selection; the two current screening modes, wire electrode and potentially permanent foramen electrode, should be compared regarding technique, predictive value, and cost-effectiveness (reimbursement in most countries hampers further expansion of the technique). The indications for SNS have been expanded beyond the field of fecal incontinence to slow-transit constipation and outlet obstruction. Preliminary data indicate that it may be beneficial [17]. Based on these findings, a prospective multicenter trial is ongoing. In the future, the study of SNS interaction with the anterior and middle compartment of the pelvis and pelvic floor will identify further conditions in which SNS can be of clinical value. The use of SNS has constantly evolved since its first application for the treatment of fecal incontinence. From selection based on conceptual physiologic considerations, it became a technique applied by a pragmatic approach. Thus the spectrum of indications expanded. However, despite the very positive clinical outcome, increased use, and broadened acceptance, our knowledge of its mechanism of action remains limited. Research should be performed on patient selection (based on defined morphologic and physiologic conditions), new indications (with the staged diagnostic approach) new techniques, long-term outcome, increased efficacy (either by technical modifications or individualized approaches based on physiologic findings), and determination of the role of SNS in the treatment algorithm. This is a dynamic process with a relatively new treatment concept; we must constantly reconsider our understanding of anorectal physiology and neurostimulation in the treatment of anorectal functional disorders.

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Neurally augmented sexual function

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Summary

Neurally Augmented Sexual Function (NASF) is a technique utilizing epidural electrodes to restore and improve sexual function. Orgasmic dysfunction is common in adult women, affecting roughly one quarter of populations studied. Many male patients suffering from erectile dysfunction are not candidates for phosphdiesterase therapy due to concomitant nitrate therapy. Positioning the electrodes at roughly the level of the cauda equina allows for stimulation of somatic efferents and afferents as well as modifying sympathetic and parasympathetic activity. Our series of women treated by NASF is described. Our experience shows that the evaluation of potential candidates for both correctable causes and psychological screening are important considerations.

Keywords: Neuromodulation; sexual function; neural augmentation; orgasmic dysfunction.

Introduction

Reproductive function is fundamental to the survival of a species. A species that cannot replace its ranks is on the path to extinction by definition. Despite this evolutionary importance, in humans, sexual dysfunction is surprisingly common. Female populations in the United States [4], United Kingdom [15], Australia [14], and Morocco [6] all demonstrate an incidence of orgasmic dysfunction, ''persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase''[4], of approximately 24%. Adult male populations demonstrate an incidence of erectile dysfunction of 15–51% [3, 16, 17, 21]. In selected male populations (''young'' elderly males undergoing therapy for cardiac disease), the incidence is reported as high as 75% [7].

The causes of sexual dysfunction, of which orgasmic dysfunction is a subset, are myriad. Anatomic ignorance may be a correctable cause. In many cases sexual dysfunction is a manifestation of an underlying disease state. Systemic diseases such as diabetes, multiple sclerosis, and hypertension are common examples. Localized infections may first present with sexual dysfunction as a chief complaint. Sexual dysfunction can present as a medication side effect. As an example, serotonin reuptake inhibitors have been demonstrated to cause decreased libido in some patients [8], an unfortunate side effect for an antidepressant. Psychological issues such as lack of rapport with a given partner or frank mental illness can also produce sexual dysfunction.

The therapy for sexual dysfunction is dictated by the underlying cause. Thus, accurate diagnosis is critical. Despite a systematic and thorough search for offending agents and occult disease, there remain large groups of individuals who cannot be successfully treated. In men, erectile dysfunction is often associated with atherosclerotic vascular disease. Nitrates are often utilized in therapy of the latter process and thus preclude the use of the cGMP phosphodiesterase inhibitors. In women, roughly half of the groups noted above will not have an identifiable cause. For these groups and other, the use of spinal cord stimulation for the treatment of otherwise uncorrectable sexual dysfunction is viable. This therapy is termed Neurally Augmented Sexual Function or NASF.

Spinal cord stimulation is the use of epidurally implanted electrodes for the treatment of chronic intractable pain. It is a practical application of the gate control theory of pain [12]. The therapy has improved rapidly with more maneuverable and durable leads and smaller percutaneously rechargeable generators. Programming capabilities have become vastly more versatile and complex. The theory of the process has expanded from the concept that only the dorsal columns of the spinal cord are being stimulated to the recognition that the entire cord can be involved in the process.

Initial observations

My first observation occurred through matter of serendipity. A female patient had been taken to the operating room for placement of a permanent spinal cord stimulator for treatment of refractory radiculopathy. Initial lead placement was congruent with the T-10 level noted at percutaneous trial. When power was supplied to the electrodes, the patient vocalized involuntarily. The initial diagnosis was that the electrodes had migrated anteriorly and that unpleasant muscular contractions had been produced. Power was rapidly removed from the unit and inquiry made to the patient as to her condition. An increase in respiratory rate, pulse, and blood pressure was noted. The patient maintained 100% peripheral oxygen saturation on nasal cannula. On initial exam she was nonverbal but appeared to be in no distress. She cleared rapidly and stated ''you're going to have to teach my husband how to do that.'' Subsequent discussion with gynecological colleagues revealed the high incidence of orgasmic dysfunction in women. An undesirable side effect of one therapy would be potentially applicable to another, very common, disease state.

Neural pathways of sexual function

Sexual function is a result of the interaction of several nerve pathways. The innervation of the genitalia is derived from the somatic, sympathetic, and parasympathetic systems. Tactile, olfactory, visual, and auditory inputs can all provide initial signals for arousal in the brain. The medial preoptic area of the hypothalumus is associated with the summation of cortical inputs that determine arousal [9], and in some cases this input is enough to generate orgasm without additional input [24]. The paraventricular nucleus has extensive interconnections with the medial preoptic area as well as contributions to autonomic tone and direct projections to both pelvic autonomic and somatic output. Tonic inhibition of the sexual spinal reflexes is provided, in part by the nucleus paragigantocellularis located in the medulla. The role of other structures, e.g. Barrington's nucleus, is unclear [10]. Higher centers include the medial preoptic, dorsomedial and ventromedial nuclei of the hypothalamus, Barrington's nucleus, Onuf's nucleus and the periaqueductal gray. While these structures are not stimulated directly in this approach, the latter is considered an important site for interpretation of sensory input from the penis [20].

McKenna has recently summarized the neuronal arrangements of sexual function in female rats:

- The autonomic innervation of the pelvic organs is through the hypogastric and pelvic nerves, providing the sympathetic and parasympathetic inputs respectively. The spinal cord in the rat is longer relatively to the spine and thus the termination extends to the sacrum. The inferiormost portion of the cord provides the origination for parasympathetic impulses. The sympathetic ganglia are located in the thoracolumbar segments. In humans, these sites are adjacent to one another.
- Motor innervation is supplied by the pudendal nerve, which also provides the sensation for the perineum, clitoris and urethra. Afferent fibers for the vagina and cervix are conducted through the pelvic nerve. Additionally vagal fibers have the potential to be involved in conducting information to higher centers.
- Within the spinal cord there are interneurons providing for sexual responses on a reflex basis. These interneurons are located in the central gray region of the cord and near the intermediolateral cell column. Most of the sexual reflexes are activated by pudendal afferents.
- Transmission to higher levels is by both spinothalamic and spinoreticular routes [10].

The parasympathetic system is primarily responsible for penile vasodilatation and tumescence [20] and vaginal vasocongestion and lubrication [18].

Mechanism of action

The neural augmentation of sexual function most likely involves both autonomic and somatic nerves.

Tumescence and ejaculation have been shown to be dependent on spinal interneurons in male rats [22]. In spinal cord injured human females, Sipski has noted that orgasm only occurs in women with intact sacral innervation. This has led her to conclude that female human orgasm is dependent on autonomic nervous system activity via a sacral reflex [19].

Although higher centers are important in erection and ejaculations, spinal reflexes have been demonstrated to result in erections; these are postulated to include interneurons between pudendal nerve afferents terminating in the medial portions of the dorsal horn and central gray matter and the dendritic zones of pudendal and parasympathetic neurons [9]. Sexual arousal and subsequent climax via NASF is a function of summation of impulses of sufficient intensity and duration that lead initially to

penile/clitoral tumescence and vaginal vasocongestion and subsequent climax as intraspinal reflexes are triggered. In this model, patients who have orgasmic dysfunction due to a raised neurological threshold, may benefit from a supranormal stimulus.

Electrical stimulation of spinal structures and peripheral nerves has been demonstrated to improve blood flow to the brain [5], heart [2], clitoris and vagina [23], but not peripheral skin [1]. Thus it is not difficult to imagine that spinal cord stimulation would alter blood flow in such a way as to produce tumescence. In male rats, Truitt and Coolen have demonstrated a population of neurons at the L3–4 levels that are critical to ejaculation [22]. Although spinal cord stimulation in women resulting in pleasurable genital parathesias has been seen as high as T-9, most commonly the electrode placement is at the L1–2 level [11].

This level is generally where the spinal cord terminates in most adults. Stimulation at this level allows stimulation of parasympathetic preganglionic axons (which are felt to be the major excitatory nervous input facilitating erection) as well as providing somatic efferent output via the pudendal nerve. Perceptually, afferent input from the terminal branch of the pudendal nerve, the dorsal nerve of the penis, enters the cord at this level.

Sympathetic innervation can also be influenced at the L1–2 level by stimulation of preganglionic fibers in the intermediolateral cell column and the intercalated nucleus. These fibers then pass via white rami comunicants to the sympathetic chain [20].

Given the complex interplay between the various nervous systems it is not surprising that only a few combinations of stimulation will have the observed effect. At present, it is not possible to say specifically how much stimulation needs to be applied to a given pathway. However various electrode placements, anode/cathode, frequency, amplitude and pulse width combinations can be undertaken, as is standard for spinal cord stimulation. Those combinations that place the stimulation primarily in the genitalia and are most perceptually pleasing to the patient are most likely to be successful.

Sympathetic stimulation tends to cause vasoconstriction of the genitalia. This in turn tends to decrease swelling in either the vagina or penis. Removal of this influence tends to favor lubrication and arousal. Spinal cord stimulation is quite successful clinically in treating cases where adverse activity of the sympathetic nervous system is felt to be responsible for the painful complaint, e.g. complex regional pain syndrome with sympathetic component. Thus it is not surprising that spinal cord stimulation would alter sympathetic output with other manifestations. It has been demonstrated that sympathetic activation, through exercise, has facilitory effects in arousal in normal women but not anorgasmic women [13]. This would lend further credence to a sympathetic component being present in orgasmic dysfunction.

From a somatic standpoint, the induced sensations are interpreted by the brain as having originated from the pelvic organs rather than from the cord per se. Fundamentally nervous information is a series of electrochemical events occurring at a given frequency and amplitude. There are, of course, an enormous number of such impulses that vary in both frequency and amplitude with respect to time, but ultimately the brain integrates them into the sensation we experience consciously as touch. The origin of the information is not identifiable from the message itself; the brain responds to a pleasurable sensation in the same manner whether the impulse originated in the periphery or centrally. Thus the somatosenory component is integrated into the region of the medial preoptic area and interpreted along with data from other sources to determine whether the condition is pleasurable. Once that determination is made tonic inhibition is reduced and facilitory centers are excited.

Employment of the electrodes at the L1–2 level places them, in most adult humans, at the termination of the spinal cord. This allows the opportunity to influence both sympathetic activity through the intermediolateral cell column and parasympathetic activity at the inferiormost portion of the cord. The induced impulses can directly stimulate the pelvic somatic nerves, and create sensory afferents for interpretation by the brain. This information can, in turn, send additional signals from the brain to the pelvic nerves. The extent that any given one of these factors governs the response is currently unknown.

Technique

Techniques for entering the epidural space and maneuvering stimulator catheter electrode arrays are discussed elsewhere. In most patients the initial electrode placement will be at the L1–2 level with the electrodes aligned with the physiologic midline. To facilitate this, entry is made into the epidural space 2–3 segments below the target. The shallowest entry angle possible is used to optimize steering of the catheter electrode array. As with most spinal neuroaugmentation, individualized variations of

electrode position and combination(s) of frequency, pulse width and amplitude are determined during the trial process. Retrograde placement of electrodes into the sacral region is another available approach. Single array midline lumbar epidural placement has been demonstrated to be successful in achieving genital stimulation in over 90% of female patients and has less morbidity.

Midline posterior epidural septae have complicated lead placement more frequently in the low lumbar positions used in this technique than is common in higher sites. Use of bilateral arrays to bracket the target or the latest generation of stimulators which allow for the use of so-called ''steerable current'' can mitigate this problem.

Electrode migration is more common during percutaneous trials in NASF patients than in the chronic pain population. The patient population suffering from sexual dysfunction differ in their underlying fitness from chronic pain patients. In general, the underlying causes of sexual dysfunction do not, in and of themselves, lead to chronic deconditioning as is often associated with patients who have a long standing history of chronic pain. Thus the ''normal activities'' that NASF patients resume tend to be more intrinsically vigourous than chronic pain patients. Sexual activity, while not considered an aerobic activity per se, does consist of repetitive ballistic motions that cannot be easily constrained at climax. Surgical fixation techniques utilized for securing the electrodes need to take these differences into account, especially in percutaneous placements.

One recommendation that has quickly emerged is the use of eight contact arrays preferentially to give a greater chance of recapture should migration occur.

Results

At present, studies of NASF are limited to an eleven female patient population. In this group pleasant genital parathesias were achieved in 10 patients. In the subset of patients with secondary anorgasmia (5/11), orgasmic function was restored with the use of stimulation for the duration of the trial in 4 patients. Thus secondary anorgasmia, defined as normal sexual function at some point in the patients lifetime, seems more amenable to therapy than primary anorgasmia (individuals who never had an orgasm). Due to the small sample size it is not possible to assign specific causes to this difference, however secondary anorgasmia is by far the more common scenario.

Spontaneous occurance of NASF in both males and females who have undergone spinal cord stimulation for chronic pain has been observed in my practice. Other practitioners have reported similar cases to me anecdotally. Patients are often reluctant to bring up the topic. The true incidence may be much greater than commonly thought.

Complications

As with any device being implanted in close proximity to the central nervous system at the level of the spine, risks of dural puncture, back ache, bleeding, infection, paralysis, nerve damage, worsening pain, numbness, spinal cord trauma, sphincter incontinence, sexual dysfunction, and death exist. There is no evidence that patients undergoing implantation for NASF have any increased risk for these complications.

One theoretical concern that has thus far proven unfounded is the idea that patients would be so enamored of the sensation that they would neglect themselves and suffer from dehydration or rhabdomyolysis. There has been no evidence of this behaviour either in study patients or patients who have permanently implanted devices. Patients who receive NASF implantation undergo psychological screening as it is standard for any patient who is being considered for spinal cord stimulation. The disease process is a phenomon of middle age and patients thus studied were selected for, among other things, stability of relationships. Given that sexual stimulation and particularly orgasm generate impulses at the dopiminergic reward center, addictive behavior is a possibility that may yet emerge. Currently it would appear that patients are able to integrate improved sexual function into their lives without difficulty.

Future

NASF represents an innovative approach to a common problem of aging. The technical placement is well within the capabilities of experienced implanters. Multicenter trials to demonstrate efficacy are being planned. At present, patients are expressing interest in both percutaneous and surgically implanted devices on an elective basis. Ultimately, there will be, most likely, two populations utilizing the device. Patients with orgasmic dysfunction and erectile dysfunction and normal patients seeking a more intense sexual experience. The experience with neuroaugmentation has shown that careful patient selection in critical to success. Neurally augmented sexual function in unlikely to be different in this regard.

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Neuromodulatory approaches to chronic pelvic pain and coccygodynia

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Summary

Intractable chronic pelvic pain (CPP) despite a multidisciplinary approach is challenging to treat. Every structure in the abdomen and/or pelvis could have a role in the etiology of CPP. Management of chronic pelvic pain may require a combination of interventions, including pharmacological, physical and psychological therapy. Interventions suggested to date include nerve blocks (ilioinguinal, iliohypogastric, genitofemoral, hypogastric, presacral) and trigger point injections, radiofrequency treatments, spinal cord stimulation (SCS), sacral root stimulation, sacral magnetic stimulation and sacral stimulation via tibial nerve. Peripheral nerve stimulation (PNS) has been particularly successful in the treatment of mononeuropathies. Indications for targeted stimulation include localised pain in non dermatomal distribution. Herein, the epicenter of the site of pain (target) is stimulated either transcutaneously or percutaneously or via permanent neuromodulating implant. Targeted and PNS probably are underused treatment modalities given the simplicity of the technique. The introduction of a stimulating electrode directly to the center of peripherally affected, painful areas, thereby bypassing the spinal cord and peripheral nerves is a novel simple procedure with effectiveness in the control of intractable neuropathic pain. Development of newer devices and miniaturization of electrodes will play a role in refinement and further simplification of subcutaneous neuromodulation.

Keywords: Neuromodulation; chronic pelvic pain; coccygodynia; peripheral nerve stimulation.

Introduction

Chronic intractable pelvic pain despite a multidisciplinary approach is challenging to treat. Its management is a subject afflicted by the failure to identify its pathophysiological origins. Chronic pain disorders, in general, are more common among women who also exhibit more frequent pain, with higher disability ratings and greater use of health care resources as compared with men [3, 7].

Population-based studies in the United States and United Kingdom have reported the prevalence of CPP among reproductive-aged women to be 14.7 and 24.0%, respectively [28]. By extrapolating the data, more than 9 million reproductive-aged women in the United States would meet the criteria for chronic pelvic pain, with direct costs of more than $2.8 billion and indirect costs greater than $555 million [17].

Definitions

Chronic pelvic pain (CPP) is non-malignant pain perceived in structures related to the pelvis of either men or women. In the case of documented nociceptive pain that becomes chronic, the pain must have been continuous or recurrent for at least 6 months. If non-acute mechanisms are documented, then the pain may be regarded as chronic irrespective of the time period. In all cases, there may be associated negative cognitive, behavioral and social consequences [7].

Chronic pelvic pain syndrome (CPPS) is the occurrence of persistent or recurrent episodic pelvic pain associated with symptoms suggestive of lower urinary tract, sexual, bowel or gynecological dysfunction. There is no proven infection or other obvious pathology [1].

Coccygodynia is the occurrence of pain in the coccyx region. The exact cause of coccygodynia is unclear. Postulations of possible pathological conditions include osteoarthritis of the sacrococcygeal joint, nonunion, subluxation, lumbar pathology, injury from delivery, gastrointestinal pathology, spasm of the pelvic floor, and functional neurosis.

Etiology

Classification of chronic pelvic pain syndrome

The axes of classification of conditions that may be considered under chronic pain syndrome is based on the International Association for the Study of Pain (IASP)

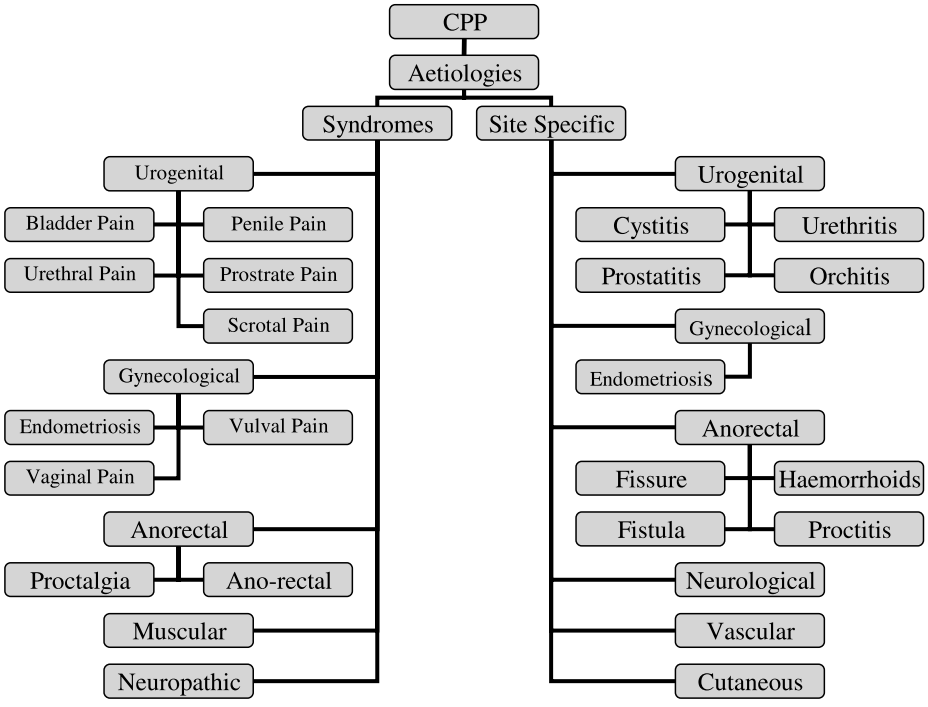

Fig. 1. Etiological classification of chronic pelvic pain

classification [19] which extends above and beyond the system to include temporal, intensity and etiological characteristics while much of the terminology comes from International Continence Society (ICS) classification of chronic pain [1].

Every structure in the abdomen and/or pelvis could have a role in the etiology of CPP. Therefore, it is essential to think beyond the organs of the upper reproductive tract and also consider contributions from the following: the peripheral and central nervous system, blood vessels, muscles and fascia of the abdominal wall and pelvic floor, the ureters and bladder, and gastrointestinal tract. Many disorders involving these organ systems are implicated in CPP (Fig. 1), including endometriosis, interstitial cystitis, irritable bowel syndrome, neurological and pelvic floor dysfunction.

Pathophysiology

Neurophysiology

Two neurophysiological mechanisms are implicated in the pathophysiology of CPP: nociceptive pain, which results from injury to a pain-sensitive structure and is somatic or visceral in origin, and nonnociceptive pain, which is neuropathic [6].

Somatic pain originates from skin, muscles, bones, and joints and is transmitted along sensory fibers; it is generally described as sharp or dull and is usually discrete. Visceral pain, on the other hand, is transmitted through the sympathetic fibers of the autonomic nervous system and could be described as poorly localized, dull or cramp [22]. Visceral pain is frequently associated with autonomic phenomena such as nausea, vomiting, sweating, and strong emotional reactions. In addition, many patients have visceral hyperalgesia, an exaggerated pain response resulting from changes induced in the central nervous system from painful stimuli. Neuropathic pain is the result of an insult to the central or peripheral nervous system and may produce burning pain, paraesthesias, dyaesthesias, allodynia or pronounced summation and painful after reaction with repetitive stimuli.

Viscero-visceral hyperalgesia

Part of the dilemma involved with the evaluation and management of CPP is the assumption that pain can be linked with some form of pathology or obvious tissue damage. Complex interactions occur among the reproductive organs, the urinary tract, and the colon. One phenomenon has been termed viscero-visceral hyperalgesia. Essentially, inflammation or congestion in the reproductive organs, either physiological from ovulation or menses, or pathological from endometriosis, could enhance pain in viscera, skin, or muscle that share common spinal cord segments [8]. This might be one of

the explanations for menstrual exacerbation of chronic pelvic pain, a common occurrence that should not be confused with dysmenorrhea.

Hormonal influence

Hormones may modulate nociceptive processesing and may be partly responsible for the increased incidence of chronic pelvic pain in women. Both oestrogens and progesterons affect the generation of pain signals from the bladder both peripherally and centrally.

This female predominance is not entirely explained by reproductive tract-induced hyperalgesia in common spinal cord segments because women also have a higher incidence of chronic pain conditions remote from the pelvis. Potential mechanisms include the effects of estrogen on neurogenic inflammation and other hormonal effects on the central and peripheral nervous systems [4].

Neurogenic inflammation

Neurogenic inflammation is the process by which stimulation of the peripheral nerves elicits vaodilation, plasma extravasation and other inflammatory changes in the skin and the viscera [20]. It results from a complex interaction between the central and peripheral nervous system and the immune system, causing the release of neuromediators that activate receptors on specific cells, including mast cells, Langerhans' cells, microvascular endothelial cells, fibroblasts and infiltrating immune cells [18].

Sensory afferents apart from being carriers of messages to the central nervous system (CNS), also act in the periphery through the release of neuropeptides. Acute neurogenic inflammation can lead to chronic changes in the innervation, resulting in a persistent pain syndrome. Blockage of nerve growth factor (NGF) prevents hypertrophy of dorsal root ganglion (DRG) cells from occurring in response to inflammation. Thus there is a firmly established relationship between secretion of NGF and alterations of nociceptive signaling in both peripheral and central sites. The role of purinergic signaling through the release of urothelial adenosine triphosphate and the stimulation of subepithelial nerve plexus via the purinergic P2X3 receptor, resulting in pain, may provide an explanation for the symptom profile seen in CPPS [26].

Pain mapping

The exact location of pain should be mapped to see if it corresponds to the distribution of the ilioinguinal/iliohypogastric/genitofemoral/lumbar root/sacral root/lumbar sympathetic plexus (L1)/superior hypogastric plexus (presacral) nerves and an evaluation of the anterior abdominal wall should be performed to identify scar pain and trigger points.

Management

Management of chronic pelvic pain may require a combination of interventions, including pharmacological, physical and psychological therapy.

Pharmacological

The World Health Organization (WHO) guidelines for pain control can be adapted for nonmalignant pain [15]. Drugs used include simple analgesics, non-steroid anti-inflammatory drugs (NSAIDs), weak or strong opioids, antineuropathic agents, local anaesthetics and anticonvulsants.

Interventions

Depending on individual treatment pathways, these may follow the pharmacological failures. However, they are also increasingly being adopted as first line management.

Nerve blocks

Nerve blocks and trigger point injections may be performed for diagnostic reasons, therapeutic benefit and or possibly both. Diagnostic blocks can be difficult to interpret and a clear understanding of multiple mechanisms by which a block may work must be understood. Consistent, albeit temporary, responses have been used as an indicator prior to application of long term measures such as a continuous catheter, neurolytic block or peripheral permanent neuromodulation.

Peripheral nerve blocks such as ilioinguinal/iliohypogastric/genitofemoral/may be useful in neuropathic pain associated with respective nerve involvement or in pain corresponding to the distribution of these nerves. Pudendal nerve blocks may be useful in the management of pudendal nerve involvement or possibly pelvic floor muscle spasm. Superior hypogastric plexus (presacral nerve) does not receive fibers from the ovaries and lateral pelvic structures, and hence, is applicable only to midline pain, while lateral pelvis transmits pain via parasympathetic neurons (nervi erigentes) arising from S2 through S4.

Radio frequency treatment

This treatment, in the form of thermal or pulsed, may be applied to the nerves involved or directly to the site of pain, while the later to the nerve roots delineating the distribution of pain.

Established neuromodulatory approaches

Spinal cord stimulation (SCS)

SCS and conus stimulation have not shown adequate long-term coverage for sacral mediated pain. This is probably due to the variability of sacral rootlet contact with the active cathode(s) (in conus stimulation) and to the depth of sacral fibres [in dorsal column stimulation (DCS)], which results in the production of painful dyaesthesias in more proximal neural structures during stimulation.

Sacral root stimulation

Sacral nerve stimulation has been described using a transforaminal approach, limiting the targets to one nerve root or pair of nerve roots (S2 or S3). Using this approach, an electrode array is passed directly into the foramen of the desired nerve root. The anatomy makes this approach problematic as the nerve exits perpendicular to the electrode array. This probably explains the variable paraesthesia coverage experienced by patients with this form of implant, as well as the 'shocking' phenomenon that some patients describe. Unilateral stimulation of sacral nerve roots (typically S3 in the case of transforaminal stimulation) has been advocated for pelvic pain, although there is some evidence for increased efficacy when bilateral stimulation is employed. The latter with parallel position electrode placement relative to the nerve (in distinction to perpendicular to the nerve), with establishment of electrical field across the sacrum (multiple sacral nerve roots) has been suggested to be more beneficial [2]. Lumbar percutaneous retrograde sacral nerve stimulation, unlike transforaminal systems, is easily able to cover S2–S4.

Recent advances

Sacral magnetic stimulation

Application of non-invasive electromagnetic therapy may have a neuromodulating effect on pelvic floor spasm and neural hypersensitivity [23]. It may reduce pain during stimulation only, without producing a sustained relief of symptoms [16]. The present results need to be interpreted cautiously because of the small, although homogenous, patient population and the lack of a control group treated with a sham device.

Sacral stimulation via the tibial nerve

It is performed by a peripherally placed neuromodulation system. Leads which are inserted near the ankle or lower tibia, has shown some success in the treatment of urge incontinence [14].

Ilioinguinal/iliohypogastric/genitofemoral nerve stimulation

PNS has been particularly successful in the treatment of mononeuropathies [5]. It is indicated when a painful body part is innervated by a single afferent nerve that lends itself to simple intermittent percutaneous stimulation [13] or lead placement in the immediate proximity of the nerve trunk. With the introduction of thin multipolar leads minor nerves can now be targeted. Recently, published studies comprise of small number of cases, but the outcomes have often been good to excellent (in the range of 60–80% success after several years follow up) [24]. Subcutaneous permanent neuromodulating electrode has been successfully implanted to the inguinal nerve for post inguinal hernia repair pain [25].

Targeted stimulation

Indications for targeted stimulation include localised pain in non-dermatomal distribution. Herein, the epicenter of the site of pain (target) is stimulated either transcutaneously or percutaneously or via a permanent neuromodulating implant (Fig. 2).

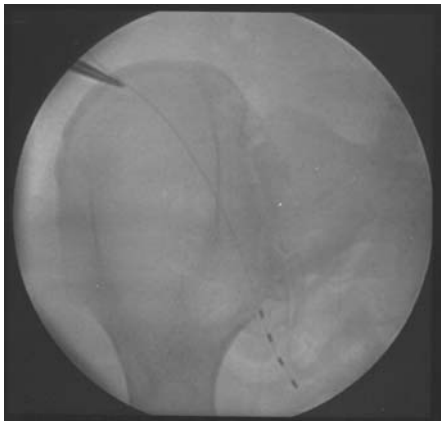

Fig. 2. Ilioinguinal/iliohypogastric nerve stimulation by Qaud electrode in situ

In coccygodynia, the authors suggest a subcutaneous placement of a permanent neuromodulating electrode directly at the site of pain [12].

Stimulation technique and evaluation

The pathway set out by the authors involves four main stages. *Stages 1–3* provide not only diagnostic but therapeutic benefit as well, albeit varying in duration. *Stage 1* involves external neuromodulation, *Stage 2* comprises of needle neuromodulation, *Stage 3* is of temporary electrode implantation and finally *Stage 4* is permanent neuromodulating implant.

Awake intraoperative assessment in the operating room during the procedure is crucial to success.

Stage 1

External neuromodulation involves the use of a transcutaneous nerve mapping probe as used in regional anaesthesia to delineate the proposed nerve or stimulate the target [19]. This is connected to a stimulating device. Paraesthesia in the distribution of pain is taken as the end point and therefore may need more than one nerve to be stimulated due the overlap in distribution by the nerves. The amplitude is adjusted to acceptable paraesthesia and stimulation continued for 5 minutes, the later chosen for standardization and practicality. Currently there is no evidence on optimum duration of stimulation.

More than 50% pain relief on a visual analogue scale (VAS) is classified as a positive response. The procedure has the main advantage of being non invasive and therefore may be performed in the outpatient department, repeated frequently and be considered for self administration by the patient. A consistent but short duration of pain relief for few hours would imply to proceed to stage 3 of temporary electrode implant trial. The thickness of the subcutaneous tissues varies in individuals and may render nerves inaccessible to external stimulation and indicate needle neuromodulation.

Stage 2

Needle testing involves a stimulating tip needle introduced percutaneously to the addressing nerve or target. The needle is then connected to a nerve stimulator. The amplitude is adjusted to cause acceptable paraesthesia in the painful area, for a set duration of 5 minutes [11]. Reduction in the pain score (VAS) by 50% is considered a positive test. The further options depend upon the duration of pain relief. The procedure can be repeated at intervals for therapeutic benefit wherein initial procedure produces pain relief lasting for more than few days. Consistent though short duration pain relief suggests progress to Stage 3.

Stage 3

A temporary neuromodulating electrode in the form of stimulating monoelectrodes (Stimulong plus, Pajunk) may be inserted percutaneously, connected to an external testing device as a pulse generator and left in situ for seven days. This should continue to provide similar, substantial reduction in intensity of pain as achieved during the initial external and percutaneous needle diagnostic tests. The monoelectrode 20G is inserted through a 19.5G needle and, therefore, is far less invasive as well as a cheaper option compared to other available stimulating electrodes.

Stage 4

This involves the placement of a permanent percutaneous neuromodulating implant. In accordance with our centre's guidelines (extrapolated from Pain Society guidelines for Dorsal Column Stimulation and applied to all Permanent Neuromodulatory implants), patients awaiting neuromodulatory implant implementation should undergo a formal psychological assessment.

The procedure is performed under aseptic precautions and antibiotic cover. Needle stimulation test (Stage 2) targeted to the addressing nerve or target is repeated but now with a larger gauge to allow passage of the desired permanent electrode through it. A custom made 15G Tuohy stimulating tip insulated needle (Pajunk) will allow passage of presently available quad and octopolar electrode. The needle is connected to a stimulator to continuously stimulate the painful areas as a confirmatory test. Through this, the desired electrode is passed which is then connected to a standard tester. Awake intraoperative testing is vital.

Mechanism of action of peripheral and targeted neuromodulation

Specific changes in post-synaptic excitation in the dorsal horn are independent of which group of primary afferent has been activated. Stimulation of Aβ fibres causes direct excitation as well as pre and post-synaptic segmental inhibition of wide dynamic range neurons with a combined duration of several 100 milliseconds.

Stimulation of A-delta fibres activates the long-term inhibitory system acting for several hours described by Randic *et al.* [21] corresponding with the up regulation of early immediate genes.

Peripheral nerve stimulation is likely to recruit larger number of nerve fibres for the purpose of activating inhibitory interneurones than SCS, which exerts its effect through layers of dura and cerebrospinal fluid. Peripheral nerve stimulation also permits recruitment of primary afferent delta fibres, which project to the spinothalamic tract and probably not to the dorsal column. These fibres will therefore not be accessible to spinal cord stimulation. PNS may thus turn out to be a more powerful method of analgesia than SCS. It is likely that a combination between both above inhibitory mechanisms is responsible for the observed pain relief.

The cumulative evidence, both anecdotal and scientific, would suggest that early rather than later implantation is much more successful in the management of pain that is neuropathic and distal in the affected nerve.

Conclusions and future potential

Targeted and peripheral nerve stimulation probably are underused treatment modalities given the simplicity of the technique. The introduction of a stimulating electrode directly to the center of peripherally affected, painful areas, thereby bypassing the spinal cord and peripheral nerves is a novel simple procedure with effectiveness in the control of intractable neuropathic pain. Development of newer devices and miniaturization of electrodes will play a role in refinement and further simplification of subcutaneous neuromodulation.

The future of the field is promising. At the present time, efforts are underway to develop more appropriate designs not only for smaller refined and remote access electrodes, but also for external transcutaneous probes, needle and multi electrode temporary catheter testing. Although there are, to this date, no randomized, prospective controlled studies to scientifically validate the therapeutic efficacy of targeted and peripheral nerve stimulation, reports during the last few years support its success.

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Functional electrical stimulation

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Neuromodulation by functional electrical stimulation (FES) of limb paralysis after stroke

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Summary

Functional Electrical Stimulation (FES) in stroke patients has been demonstrated to provide clinical benefits such as improvement in movement, skills, function and decrease of spasticity. Imaging and neurophysiological studies have shown cortical excitability and reorganization. After injury, the parameters of timing, intensity, frequency, and duration of FES are still to be determined. Additional issues that should be determined are whether the changes induced by FES are long-lasting, and which clinical and electrophysiological parameters are important and to what extent.

Keywords: Neuromodulation; FES; functional electrical stimulation; limb paralysis; cerebral palsy; stroke.

Introduction

Hand total or partial paralysis, contralateral to the insult, is a common result of a brain stroke. During the 1.1.03–31.12.04 period, of the stroke patients admitted to our department of neurological rehabilitation, 31% suffered from upper limb paralysis and 55% of partial paralysis [37]. These patients also frequently suffered from superficial and/or deep sensory impairments affecting both the hand and limb sensory/motor integration and function. In addition, they suffered from different degrees and patterns of altered muscle tone, i.e. spasticity. Only a limited number of patients improve either spontaneously or because of treatment. Hand paralysis results in diminished functional capacity in activities of daily living (ADL), pain, and discomfort. In many cases, it also leads to mood disorders secondary to the disability such as depression, anxiety, etc.

Rehabilitation following hemiplegic stroke has typically emphasized the reestablishment of function in mobility and ADL by training the patients in compensatory strategies. The neurological deficits and the potential for recovery have often been considered a matter of self-healing of those neural elements that have suffered only partial injury, and cannot be affected significantly by physical treatments. This approach is based on the concept of the brain being ''hard-wired'', with the homonculous being the unique motor and sensory brain representation of the body. However, an ever-expanding body of basic science and clinical research strongly demonstrate that these beliefs are no longer tenable.

In recent years, a trend of research and clinical trials on FES, mainly of the hand, has attracted renewed interest. The FES experiments were started by Lieberman in the sixties, but for several decades the developments were minimal, most likely because of technical limitations. In recent years, improvements in both technology and software have allowed investigators to perform much better research. Hence, there are now better and promising results for stroke patients. In our research on FES in stroke patients [38, 47], improvements have been found in hand movements, hand and upper limb function in ADL, the reduction of spasticity and decrease or termination of pain (mainly paretic shoulder pain). An interesting observation, relevant to neuromodulation is that many of the improvements in function, appeared not as a direct result of electrical stimulation but followed the end of the FES trial, sometimes after several months. These findings had a strong impact on the research in the complex problem of hand paralysis. Traditionally, we have been taught that brain neurons do not regenerate after cell death and there is little that can

be done that would result in clinical improvements after stroke. The spontaneous improvements that have been observed at later stages after stroke have been attributed either to resolution of perilesional edema or to activation of secondary neuronal centers taking over the function after the primary ones ''perished''. Recent studies including advanced imaging techniques [39] have shed light on mechanisms that differ from our classical concepts regarding neurological repair and adaptation to injury. These findings lead to new approaches regarding FES and its potential for offering additional gains in stroke patients. The cumulative evidence on FES points to the following significant finding: the central nervous system (CNS) is sensitive and reactive to peripheral stimuli and responds by temporal and topographical reorganization in the brain. This fact should be the central concept of rehabilitation strategies in the future.

In the last few years, the promise of targeting brain plasticity in rehabilitation has become a reality. In both laboratory and clinical studies, it was demonstrated that this could be a really important factor in the therapeutic process for improving neurological impairments. In order to study the compensation occurring in areas of the human brain after injury, researchers have utilized PET scans, functional MRI, focal magnetic stimulation, and high-resolution electroencephalogram (EEG). Dendritic volume, synaptic density, brain microstimulation, and intracellular recordings have been used in laboratory models.

Animal experiments

The presence of functional motor cortical reorganization has been demonstrated in experimental stroke in primates [30, 31]. It was found that motor representation may spread to brain areas previously uninvolved in the currently paretic movement but originally activated for movements in other areas of the body. In addition, the loss of brain territory, responsible for a paretic movement, decreases by early retraining and increases when retraining is withheld. The functional reorganization is accompanied by behavioral recovery. Friel *et al.* [13] studied whether the restriction of the unimpaired hand was sufficient to preserve the hand cortical area after the insult. They found that the preservation of hand cortical area requires repetitive use of the impaired hand and not simply restriction of the unimpaired hand. Abo *et al.* [1] working with rats, applied electrical stimulation two weeks after the induced lesion and utilized fMRI to examine the function. They found that two normally inactive brain regions became activated: one in the non-damaged contra-lateral sensorimotor cortex and the other one adjacent to the lesion. Luft *et al.* [26] investigated the importance of somatosensory input on the motor cortex excitability and function by stimulating the sciatic nerve in rats for two hours. They found that the amplitude of motor response to transcranial magnetic stimulation (TMS) significantly increased in the stimulated limb after somatosensory stimulation and persisted beyond the duration of the stimulation, reflecting augmented motor cortex excitability. There was a significantly smaller effect in the non-stimulated limb. This effect was not seen in unstimulated control animals or to subcortical stimulation.

Other experiments combined direct cortical electrical stimulation with rehabilitative procedures. Adkins-Muir and Jones [2] induced lesions in the motor cortex of rats previously trained to perform a skilled fore-limb reaching task (the Montoya staircase test) and then submitted the rats to 10 days of rehabilitative training, starting 10–14 days after the lesion. In addition, they implanted perilesional electrodes and evaluated the relearning of the task. A positive effect was noted in the 50 Hz stimulation group, but not in the 250 Hz stimulation group. In addition to the motor task improvement, the 50 Hz group also exhibited beneficial changes in biological parameters; in the perilesional cortex, they observed increases in surface density of dendritic processes immunoreative to the cytoskeletal protein micro-tubule-associated protein 2. They concluded that the combination of direct cortical electrical stimulation to rehabilitative training improves functional outcome and cortical neuronal plasticity after damage [2]. Kleim *et al.* obtained also similar results [20]. Similar experiments in monkeys trained to perform a unimanual motor task were conducted by Plautz *et al.* [32]. After training, a lesion to the hand cortical motor area was induced and surface electrodes were placed over the peri-infarct area. After several months of spontaneous recovery, subthreshold electrical stimulation was combined with rehabilitative training for several weeks. A significant improvement in motor performance, persisting for several months, as well as large scale emergence of new cortical hand representation in the peri-infarct area were seen.

Frost *et al.* [14] investigated the mechanism of self-repair after an induced stroke to the hand cortical area in adult squirrel monkeys. Five animals with vascular damage to the hand primary cortex were observed regarding motor performance and cortical hand representation by means of an intracortical microstimulation mapping.

They found improvements in motor performance and enlargement of hand representation in the remote ventral premotor hand area by 36% (range: 7.2–53.8%). They also found that the bigger the lesion, the greater the plasticity in intact areas, namely a greater sparing of the hand area in the motor cortex resulted in smaller expansion of the hand area in the ventral premotor cortex and vice versa. All the above represent a powerful evidence of the dynamic changes that occur after a brain lesion as well as the potential effect that stimulation and training can exert on the affected limb. According to Nudo [29], ''these recent advances set the stage for the development of new and more effective interventions in chronic stroke population that are based on the basic mechanisms underlying neuroplasticity''.

FES-induced neuromodulation in clinical trials

Normal subjects

A study using focal TMS demonstrated rapid brain reorganization in response to electrical peripheral nerve stimulation (PNS). The study in human subjects without brain disorders, measured the area of motor evoked potential (MEP) prior to and after PNS and showed an increase in MEP amplitude following PNS [35]. As the F-wave responses remained stable, the authors concluded that the increase in amplitude caused by PNS was mediated by a change in excitability of the primary cerebral cortex. In another study, the pairing of median nerve stimulation with TMS increased the amplitudes of motor responses. The plasticity evolved within 30 minutes, persisted for at least 30–60 minutes and was topographically specific [42]. Another study showed differential inhibitory and facilitatory effects on antagonist forearm muscles following 30 minutes of stimulation of the flexor carpi radialis (FCR). The MEPs from the FCR were significantly reduced, while the MEPs from the extensor carpi radialis were significantly increased, while there was no change in the MEPs of the 1st dorsal interosseous [44].

Muller *et al.* [27] studied EEG changes in healthy volunteers during wrist movements induced either by FES (in the appropriate forearm muscles) or during active and passive movements as in normal conditions. Significant EEG changes were registered both in event-related desynchronization (ERD), immediately after starting FES, as well as in event-related synchronization (ERS) after it. These findings support the view that sensorymotor processing during FES involves some of the processes that are also involved in voluntary hand movements; this is an important observation with clinical significance for rehabilitation. MEPs elicited by TMS from different hand muscles, during 2 hours of ulnar PNS, were used by Kaeglin-Lang *et al.* [17] to study the underlying mechanism of increased corticomotor excitability after somato-sensory stimulation in humans. MEPs amplitudes, recruitment curves (RC), intracortical inhibition (ICI), intracortical facilitation (ICF) and resting and active motor thresholds (rMT, aMT) serve as control parameters. The results of their complex paradigm support the view that somatosensory stimulation elicits a focal increase in corticomotorneuronal excitability that outlasts the stimulation period and probably occurs at several cortical sites. Pyndt and Ridding [34] applied the ''associative stimulation'' technique, i.e. paired electrical stimulation to the motor point of two hand muscles combined with TMS; this resulted in increased MEP amplitudes associated with ICF and short-interval intracortical facilitation (SICF), but with no changes in ICI. Charlton *et al.* [9] demonstrated persistent increased excitability of the motor cortex in response to three different protocols of PNS, including hand intrinsic motor point stimulation. In this field, of stimuli-induced modulation of intracortical excitability in normal subjects, Ridding *et al.* [36], investigated whether changes in short-ICI (SICI) following digit stimulation exhibited topographic specificity. They found that appropriately timed cutaneous stimuli are indeed capable of modulating SICI in a topographically specific manner; hence, the selective decrease in SICI seen during cutaneous stimulation may be important for focusing of muscle activation during motor tasks. Smith *et al.* [41], applied neuromuscular electrical stimulation (NMES) over the dominant quadriceps muscle (right) in ten healthy subjects and sham-stimulated controls; they used fMRI with a stringent imaging analysis methodology [15] and looked into the dose-response relationship. They used four intensity levels of stimulation and concentrated on five areas of interest (AOI) in the brain including the cingulate gyrus, thalamus, and cerebellum. Their data indicated a dose-reponse relationship between the NMES and brain activation in the AOI.

Stroke patients

The intensive use of FES, as a rehabilitation treatment modality, has improved the neurological outcome compared to the standard rehabilitation therapy [38, 33]. Growing evidence in recent years indicates that the fa-

vorable effects of FES in stroke patients may well be related to its intensive use and its use at home [6, 46]. Hirashima and Yokota [16] examined in 12 healthy volunteers and 4 patients with localized brain lesions (pontine and thalamic), the changes in MEPs after PNS at wrist; they concluded that the loss of late MEP potentiation in these locations is caused by alterations of the motor cortex excitability and that the thalamic nuclei (lateral and ventro-lateral) have an important function in the processing of peripheral sensory input for tuning motor cortical excitability.

In 31 subjects with severe acute hand paralysis following a stroke in the middle cerebral artery territory, Delvaux *et al.* [11] used focal TMS to test corticospinal excitability changes and reorganization of first dorsal interosseus (FDI) muscle motor cortical representation. They measured motor threshold, MEP amplitude, excitable cortical area, hot spot and center of gravity of FDI motor maps in both affected and unaffected hemispheres. They observed that the brain insult induces a transient hyperexcitability of the unaffected motor cortex. In addition, the temporal evolution of the FDI motor maps mostly reflects corticospinal excitability changes but also reveals some degree of brain plasticity. More interestingly, most modifications occurred within 3 months of stroke onset, paralleling the typical clinical course. In a controlled study of intensive FES at home in chronic stroke patients over a period of three weeks, the treated group had significant improvements in grasp and release hand tests, while the sham treatment group did not change. Furthermore, follow-up fMRI and a finger-tracking task showed that the cortical intensity index in the ipsilateral somatosensory cortex increased significantly after treatment. These findings suggest that intensive FES may have an important role in stimulating cortical sensory areas and making possible improved motor function [19]. In patients with chronic severe hemiparesis, the potential for improvements in upper limb functional tasks by the use of neuroprosthesis has also been demonstrated [5].

Effects of FES on neuronal plasticity: underlying mechanisms

The specific molecular signals that initiate functional reorganization of synaptic pathways have not yet been elucidated. There is evidence that neurotrophins may be a significant component of remodeling [43]. It has been reported that neurotrophins are secreted in an activity-dependent manner and increase after both peripheral nerve trauma and brain injury. These trophic factors promote neuronal survival, and regulate synaptic transmission, stability and efficiency in both developing and mature synapses [40]. They have been identified as being important for long-term potentiation, and the maturation of synapses [25]. It has been suggested that functional electrical stimulation may cause central neurotrophic enhancement; this promotes cell survival and axonal growth, permits terminal synaptic connections and facilitates synaptogenesis and neurogenesis [18]. The repetitive activation of the anterior horn cells by means of retrograde conduction from the site of stimulation is likely to generate the synaptogenic neurotrophins. The repetitive activation of paretic body segments can provide the necessary ''sensory amplification'' to initiate the remodeling process by accessing existing potential pathways and possibly promoting synaptogenesis [3].

Animal studies [10] showed that voluntary exercise increases the levels of brain-derived neurotrophic factor, improves learning and stimulates neurogenesis. In addition to this increase of brain-derived neurotrophic factor, exercise mobilizes gene expression profiles that are predicted to promote brain plasticity. After cortical stimulation in rats, Adkins-Muir and Jones [2], as mentioned above, found an increase in surface density of dendritic processes immunoreative for the cytoskeletal protein micro-tubule-associated protein 2, in the perilesional cortex. However, as Celnik and Cohen [8] have pointed out the enhanced understanding of the mechanisms of plasticity have thus far led to only few research efforts for translating these advances of basic sciences to the formulation of new rational strategies for promoting recovery of function in humans.

Discussion

Modern integrated technology [39] has allowed us to understand better the cerebral mechanisms activated after damage to a certain brain area. The recovery is usually the result of gradual adaptive changes, mainly in the somatosensory and motor areas, both in the affected and non-affected hemispheres. During the learning of new skills, relevant cortical regions become represented over larger cortical territories [28], occasionally extended to areas different from those of normal subjects [21]. Ward stated that these changes may provide the substrate whereby the effects of motor practice or experience can be more effective in driving long lasting changes in the surviving brain motor networks [45].

As described above, peripheral stimuli of various types (subthreshold sensory stimulation, constraint-induced movement therapy, FES) will trigger, speed-up and reinforce these processes of cortical reorganization, enhance brain hyperexcitability and intracortical facilitation that occur also spontaneously, thereby increasing the likelihood of improvements in the final results of the spontaneous recovery. Of all these approaches, FES seems to be the most promising. There are relatively minimal barriers for clinical implementation of a FES treatment program; the parameters and sites of stimulation can be determined in advance and be changed over time according to the progress of recovery, and most importantly, the patients can safely and efficiently use FES at home for long hours of training with good clinical results [5, 6, 38, 47]. Many patients maintain latent sensorimotor function that can be realized any time after stroke with a pulse of goal-directed therapy and the use of new promising adjunct approaches including practice with robot, virtual reality, FES and drugs [12]. The imaging techniques may help to determine the capacity of residual networks to respond to therapy. Nevertheless, several critical questions on the use of FES (NMES) arise such as timing and intensity [4, 7]. The relationship between the cortical changes detected by imaging and/or TMS and the clinical ones should also be more accurately clarified. Most of the electrical stimulation studies have shown benefits in task-dependent activities rather than in generalized function and this issue should be further investigated. In the future, protocols that take into account an evidence-based rational and the above described mechanisms of neuromodulation and recovery should be introduced in neurological rehabilitation [22, 24].

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Neuromodulation of effects of upper limb motor function and shoulder range of motion by functional electric stimulation (FES)

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Summary

Upper extremity motor impairment is a major contributing factor to functional disability of stroke patients. Functional electric stimulation (FES) is one of the therapeutic regimens for the management of upper extremity dysfunction after stroke. This review shows that therapeutic FES intervention on supraspinatus and posterior deltoid muscles for 6 weeks is effective to speed up upper limb motor recovery in hemiplegia of short-duration after stroke or less severely affected symptoms. The positive effect of FES could be attributable to neural mechanisms including: an enhanced information flow from the joint and muscle afferents, a better visual perception of the movement produced, and a stronger muscle contraction due to direct stimulation of the motor neuron. However, FES was demonstrated as not being effective in reducing the shoulder range of motion of external rotation in patients with either short- or long-duration hemiplegia. In order to offer better management in maintaining or improving limited shoulder range of motion, other types of electrical stimulation should be considered.

Keywords: Functional electric stimulation; motor recovery; range of motion; arm; stroke.

The activity in one neural pathway may modulate pre-existing other activities through synaptic interaction [22]. Neuromuscular electrical stimulation (NMES) was first described over 40 years ago [26]. The afferent stimulation has been used to improve motor function in stroke rehabilitation. In theory, increased inflow of signals from sensory modalities could enhance plasticity of the brain and may generate partial beneficial effects of this treatment to other pre-existed activities [32]. Application of an electrical current to the skin stimulates lower motor nerves and muscle fibers resulting in improved contractility and greater muscle bulk [2]. Decreased spasticity and sensory cortex activation occur via afferent neuron stimulation, with additional information being provided by the proprioceptive and visual perception of NMES induced joint movement [12, 13, 24]. Clinical reports have suggested that NMES can improve muscle group strength, joint malalignment, muscle tone, sensory deficits, pain-free range of passive humeral lateral rotation (PHLR), and self-reported pain intensity [7, 14, 29, 30]. Functional electric stimulation (FES), which applies low frequency ES, aims to maintain muscle bulk and tone in the flaccid shoulder and possibly enhance functional recovery through cortical feedback [16]. It has also been suggested to provoke contraction of a paralysed muscle and to affect the sensory pathway contributing to the normalization of basic reflex motor activities [24]. Some studies have used FES to prevent the development of subluxation in the flaccid shoulder [14, 27], while others have aimed for reversal of existing subluxation [7, 10, 23]. FES has been applied either to the posterior deltoid or supraspinatus muscles [23] or to both [7, 14, 27]. Stimulation in these studies was continued for four to six weeks but the actual regimen and number of hours per day varied markedly among these studies.

Effects on upper limb motor function

Upper extremity motor impairment is a major contributing factor to functional disability of stroke patients [19, 28, 35]. At present, treatments covering a broad range of neuro-facilitatory techniques are used to improve motor control [9]. However, the results of these therapeutic regimens appear to be disappointing in many cases, especially to the functional ability level of the paretic upper extremity [19, 25]. On the other hand, in recent years, FES has been applied in the management of upper extremity dysfunction after stroke.

The study of Sonde *et al.* [32] showed that motor function increased significantly in the FES treatment group, compared to the control group. In this study, 44 patients who had a paretic arm as a consequence of their first stroke were studied and randomly assigned to either a treatment group ($n = 26$) or a control group ($n = 18$). Patients in both groups received physical therapy, usually twice a week. The treatment group received, in addition, low-electrical stimulation for 60 min, 5 days a week for three months. In order to study further the treatment effect in two levels of motoric deficit; each group was divided according to the Fugle-Meyer (FM)-score into patients with more severely affected arms (low FM-scores: 0–29) and patients with less severely affected arms (FM-scores: 30–50). Motor function in treated less severely affected patients ($n = 12$) improved significantly more than that in control group patients ($n = 9$). However, the difference was not significant in the more severely affected patients. Faghri *et al.* [14] used FES to treat shoulder subluxation in stroke patients. They also evaluated the effectiveness of FES treatment program on motor recovery. Twenty-six recent hemiplegic stroke patients with shoulder muscle flaccidity/paralysis were randomly assigned to either a control ($n = 13$) or experimental group ($n = 13$). Both groups received conventional physical therapy. The experimental group received additional FES therapy where supraspinatus and posterior deltoid muscles were stimulated to contract up to 6 hrs per day for 6 weeks. According to their results, the experimental group showed significant improvements in arm function, and electromyographic activity of the treated muscle. Linn *et al.* [27] also investigated the early electrical stimulation on prevention of shoulder subluxation and on motor function. The supraspinatus and posterior deltoid muscles were stimulated 4 times each day, with a minimum of 2 hrs between sessions. The length of each session was increased gradually, starting at 30 min in week one, 45 min in weeks two and three, and 60 min in week four. No significant difference was recorded between the groups in motor recovery as measured by the upper arm section of the Motor Assessment scale. The totally different conclusion drawn from this study, compared to the earlier cited study of Faghri *et al.* [13, 14], may be attributed to the fact that the stimulation protocols of the two studies are different: 4 times intermittent treatments each day compared to one 6-hr treatment each day. Also, the treatment duration was shorter: 4 weeks compared to 6 weeks.

More recently, Wang *et al.* [36] investigated the effectiveness of FES programs on upper limb motor recovery in patients with acute (post onset duration < 21 days) and chronic stroke (post onset duration >365 days) in a random controlled trial. The experimental groups of both short and long duration groups received FES therapy in which the supraspinatus and posterior deltoid muscles were induced to contract repetitively up to 6 hrs a day for 6 weeks. Subjects in the experimental group of short-duration hemiplegia showed significant improvements in motor recovery as indicated by Fugl-Meyer scores compared to the subjects in the control group. Such significant improvement did not occur for the experimental group of long-duration hemiplegia.

Ada and Foongchomcheay [1] examined the effect of FES on upper limb function by pooling post-intervention data from the four early electrical stimulation trials that measured function using upper limb scales [13, 14, 27, 36]. The scales included the Bobath assessment chart [13, 14], MAS scale [27], and Fugle-Meyer [36]. These scores were converted to weighted percentage for comparison. The weighted percentage difference between means suggests that early electrical stimulation plus conventional therapy is superior ($p = 0.05$) to early conventional therapy in increasing function by 19% (95% CI: 0–37). The effect on late upper limb function was also examined by pooling change data from two late electrical stimulation trials; isometric abduction strength was measured in Newtons [23]. The weighted difference between means suggests that late FES plus conventional therapy increases abduction strength by 14.4 Newton; however, the 95% CI (−5.4–34.2) indicates that there is no evidence to show that late FES plus conventional therapy is superior ($p = 0.15$). This systematic review demonstrates that there is an evidence to support the efficacy of early FES as an adjunct to conventional therapy to increase upper limb function. The positive effect of FES could be attributable to neural mechanisms including an enhanced information effect from the joint and muscle afferents, a better visual perception of the movement produced, and stronger muscle contraction due to direct stimulation of the motor neuron. According to the study of Sonde *et al.* [32], patients in the treatment group showing improvement also had intact deep and superficial sensory function, which is probably of great importance to improving motor function. Electrical stimulation does not seem to improve sensory function, but might help to optimize remaining motor control mechanisms. Another explanation of the positive results of afferent stimulation could be that the nerve impulses from the paretic area are excited to a higher level and therefore result in improving the functional recovery

possibility of partially denervated nerve cells surrounding the infarct zone. It is also believed that afferent stimulation may use the brain's plasticity and capacity for reorganization [11, 20].

Motor learning, defined as the learning of new motor skills with an intact central nervous system (CNS), requires a complex interplay between the afferent and efferent systems [4, 33]. Motor recovery, on the other hand, is defined as the recovery of learned skills after an injury to the CNS. The motor recovery and the motor learning probably share similar underlying mechanisms. The existence of the linkage between the motor learning and motor recovery is demonstrated by the expression of c-fos [15]. Cutaneous electrical stimulation has been shown to induce the c-fos expression in the spinal cord dorsal horn of rats [21]. Animal studies suggest that the afferent system has a significant role in both processes. Asanuma and Keller [5, 6] further suggested that proprioceptive and cutaneous impulses associated with repetitive movements, as stimulated by the FES, induce long-term potentiations in the motor cortex. These potentiations then modify the excitability of specific motor neurons and facilitate motor learning with subsequent functional reorganization of both cortices [5, 6]. The afore-mentioned mechanisms may be involved in the activation of pattern recognition areas, leading to the development of neuromotor engrams in the sensorimotor cortices related to FES-triggered movements. It is concluded that therapeutic FES intervention on supraspinatus and posterior deltoid muscles for 6 weeks can be used to speed up upper limb motor recovery for stroke patients with hemiplegia, for patients with short-duration or less severely affected symptoms. Although spontaneous neurological improvement can not be ruled out completely during the early intervention, the improvement is believed to be greatly enhanced by the FES treatment.

Effects on shoulder range of motion

Limitations of hemiplegic upper limb movement and shoulder pain, among others, are common serious complications of stroke patients. Complaints of pain are commonly observed when passive motion is attempted at the shoulder joint, especially in external rotation. Improving or worsening of pain is often reflected by an increase or decrease of passive range of motion [17, 18]. Painful, limited joint range of motion interferes with the use of arm in functional activities and often prevents a patient to fully participate in rehabilitation [3, 17, 18]. During the stage of absent muscle function, prolonged and progressive stretching of the joint capsule will frequently result in irreversible damage to the capsule, which causes pain and limited range of motion, especially on the shoulder lateral rotation. According to Faghri's studies [13, 14], the average passive shoulder lateral rotation for the stroke-affected side was less than that for the unaffected side in both FES and non-FES groups. In the experimental FES group, the magnitude of the differences between the affected and unaffected shoulder increased marginally (from 21 to 24°) after an early 6-week FES treatment program. Whereas for the control non-FES group, the passive external rotation range of affected shoulder deteriorated significantly when compared with the un-affected side (the difference between the affected and un-affected side was 19° at the beginning and 43° at 6-weeks). Thus, it indicated markedly less restriction on the side affected by stroke in the treatment group. However, deterioration was noted following the withdrawal of electrical stimulation, although not back to the pretreatment levels. Linn *et al.* [27] also measured the pain-free range of passive shoulder lateral rotation to investigate the effect of FES on shoulder pain; a loss of range indicated an increase in pain. They noted that both the treatment and control groups demonstrated a loss of passive range of lateral rotation over the 4-week intervention period. A greater reduction was seen in the control group, but not to a significant level. Also, the overall change over the total study period (12 weeks) showed no difference between the two groups.

Wang *et al.* [36] further examined FES applied on hemiplegic patients of short and long post-onset duration, for the purpose of investigating the FES effects on shoulder range of motion. The results showed the FES did not improve the passive range of motion of shoulder external rotation in patients with either short or long post-onset duration. This meant the early or late FES intervention is not effective to increase passive range of motion, or in other words, to reduce pain. The authors also found that the limitation in shoulder external rotation range, experienced by hemiplegic patients, is related linearly to the initial degree of the subluxation; such limitation is not reduced even if the subluxation is improved by FES treatment. Ada and Foongchomcheay [1] reviewed the prevention of pain by pooling post intervention data from four early electrical stimulation trials that measured pain-free passive shoulder external rotation [13, 14, 27, 36] using goniometer. The weighted difference between means suggests that early electrical

stimulation plus conventional therapy only maintains 4° of pain-free passive shoulder external rotation after stroke and the 95% CI (−1.2–8.6) indicates that there is no evidence that it is superior ($p = 0.14$) to early conventional therapy. In other words, according to this meta-analysis, an early FES intervention can not maintain shoulder passive range of motion of external rotation. This finding is in contrast with the previous review by Price and Pandyan [31]. However, Price and Pandyan [31] included a trial where the electrical stimulation produced only sensory response [25] as well as those that produced motor response [14, 27]. By definition, FES is an electrical stimulation of muscle deprived of normal control to produce functionally useful contraction. The electrical stimulation that produces only a sensory response can not be termed as FES, and if the electrical stimulation only aims to reduce pain [16] is not FES. At present, FES was demonstrated not effective in reducing shoulder range of motion of external rotation for patients of both short- and long-duration hemiplegia. In general, most FES studies evaluated pain by assessing passive pain-free external rotation range of motion. Unfortunately, the pain-free external range of motion was evaluated very differently, which explains the existence of wide range of studied results of hemiplegic shoulder pain reported in the literature [8, 34]. Passive pain-free external range of motion tends to overestimate the incidence and severity of pain because the level of pain experienced can increase when a shortened muscle is stretched, or if soft tissue is impinged between the humeral head and acromion process on movement. The existing approach may introduce an artificial environment, which is not relevant to patient's routine daily activity [37]. If the effect of FES on pain is to be systematically studied, a direct way of measurement of pain needs to be provided.

For better management of maintaining or improving limited shoulder range of motion in stroke patients, other types of electrical stimulation treatment mode should be considered. Increasing the range of motion is possible by using electrical muscle stimulation. Electrically stimulating a muscle contraction pulls the joint through the limited range. The continued contraction of this muscle group over an extended period of time appears to make the joint and muscle tissue modified and lengthened. To accomplish this effect, FES must be applied long enough at a sufficient current intensity to make a muscle reach a level that it can contract strong enough. This muscle then is capable to move the body part through its antigravity range. Intensity should be increased gradually during treatment [16]. However, the intensity of FES program for hemiplegic shoulder is set to obtain the desired motion of humeral elevation with some abduction and extension to pull the head of the humerus into the glenoid cavity. Such intensity and muscle exercise aim mainly to reduce shoulder subluxation. This review demonstrates that there is clear evidence to support the efficacy of early electrical stimulation as an adjunct to conventional therapy for increasing upper limb motor recovery. But this treatment is not effective for maintaining shoulder passive range of motion. Late FES can only result in minimal effects on both upper limb motor function and shoulder passive range. The jury is still out, however, on other applications of functional electrical stimulation.

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Neuromodulation of lower limb monoparesis: functional electrical therapy of walking

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Summary

After Cerebro-Vascular Accident (CVA), restoration of normal function, such as locomotion, depends on reorganization of existing central nervous system (CNS) circuitry. This capacity for reorganization, generally referred to as plasticity, is thought to underlie many instances of functional recovery after injury as well as learning and memory in the undamaged CNS. Both the reorganization of the supraspinal and spinal circuitry are highly important for the recovery of walking. The neural mechanisms responsible for learning and adapting processes are thought to involve changes both in the efficacy of synaptic function and the pattern of synaptic connections within neural circuits. In the uninjured CNS, these changes occur as a result of alterations in the amount of neural activity within circuits and are, therefore, termed activity-dependent. In this chapter, we will present several therapies of walking that provide effective input for the training of the existing CNS circuitry; thereby, contribute to long term recovery of sensory-motor functions. The focus of this chapter is Functional Electrical Therapy (FET) of walking, that is, the multi-channel electrical stimulation of sensory-motor systems that lead to more normal stance and swing of the paretic leg during the walking exercise.

Keywords: Neuromodulation; functional electrical stimulation; FES; lower limb monoparesis; rehabilitation; walking.

Introduction

Cerebro-Vascular Accident (CVA) results in impairment of the sensory-motor systems, language, cognition, and many other functions. CVA results in an initial loss of motor functions followed by abnormally active proprioceptive responses, which are clinically recognized as more brisk tendon reflexes and increased resistance to passive stretch. In many cases, this sensory-motor disability is followed by major movement disability and weakness of one side of the body. The outcome of a CVA is called hemiplegia, functionally noticeable as paralysis or paresis in the contralateral to the CVA side of the body. Hemiplegic patients undergo recovery, but only few regain sensory-motor functioning comparable to the one before CVA. Sensory-motor recovery is progressive and typically plateaus at about six months after the onset. Termination of motor rehabilitation was often recommended as patients with CVA reach plateau, that is, when the positive response to motor rehabilitation becomes marginal. Managed-care programs frequently restrict care to acute and sub-acute patients. When neuromuscular adaptation occurs in exercise, rather than terminating the current regimen, a variety of techniques (e.g., modifying intensity, attempting different modalities) should be used to facilitate neuromuscular adaptations. It was suggested that by modifying regimen aspects it might be possible to overcome the adaptive states (e.g., intensity, introducing new exercises) [24, 31].

Plasticity of the supraspinal structure of CNS has been recognized as a part of the structural and physiological substrate for recovery of function after CVA. Corticomotor reorganization could occur as a response to: altered inputs to the cortex, as an adaptation to injury of the central nervous system, as a consequence of the motor task performed, and may be either short or long term. An important element is that movement becomes more skilled with learning, and this is probably due to improvement of timing, tuning, and coordinating muscle activation. From this point of view, training of movement in hemiplegic patients could be understood as the training of the brain. The appropriately trained brain is likely to minimize the compromised loss of descending neural pathways.

Therapies leading to recovery of walking

Restoration of walking is important because the mobility is often instrumental for reintegration of hemiplegic patients into the normal daily activities. Hesse *et al.* [16] reported that three months following a stroke, approximately 20% of stroke survivors remain primary wheelchair users, and walking is limited in another 60%. We review here the orthotic methods that have therapeutic effects; thereby, lead to better walking and ultimately better quality of life. The review includes the following therapies: 1) strength training; 2) splinting of the lower extremity; 3) functional electrical stimulation (FES); 4) treadmill walking training with and without body-weight support; 5) walking assisted by a robotic system; and 6) functional electrical therapy (FET).

Strength training

Unilateral weakness following stroke is well known and well described in the literature. Weakness has been defined as inadequate capacity to generate normal levels of muscle force. Weakness is a prominent concern in hemiplegic patients; yet, it is sometimes overshadowed by concerns about treatment of spasticity and synergistic movements. Given that weakness is a common source of impairment and subsequent disability, it is somewhat surprising that more research has not been done on strength training as a therapeutic approach. Two Randomized Clinical Trials (RCT) provided important evidence that a program of strengthening exercise can improve both gait efficiency and the ability of the patient to perform activities of daily living [9, 17]. Because the number of subjects were small, this constitutes only moderate evidence that the efficiency of gait, as measured by distance walked during the fixed period of time, significantly improves after strength training.

Splinting the lower extremity

It is common practice to use splints in the hemiplegic lower extremity in an attempt to improve the gait quality. The CVA results in gait deviation, including knee and hip extension and ankle plantar flexion, during the stance phase. In order to facilitate the swing phase of gait, an ankle foot orthosis (AFO) is often used to compensate for excessive ankle plantar flexion and a lack of knee flexion. Kosak and Reding [21] found that aggressive bracing that assisted walking resulted with recovery that was better compared with the recovery that followed conventional therapy. In a RCT, Chen *et al.* [7] noted

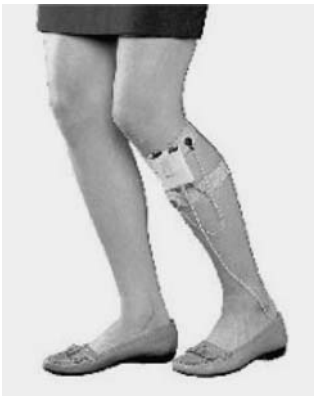

Fig. 1. FET applied to treat the drop-foot in a hemiplegic patient. Cotas 2000A®, Denmark

significant improvement in postural stability with lateral weight shifting and weight bearing through the affected side. Other non-RCTs noted improvements with AFOs in various parameters of gait. Therefore, there is limited evidence that AFOs improve elements of gait. The splinting was mostly considered as an orthotic system, and the evidence on therapeutic effects was very small or neglectable.

Functional electrical stimulation – drop-foot correction

FES in the lower extremity has been used to enhance ankle dorsiflexion during the swing phase of gait. Implanted and surface FES devices (Fig. 1) actively correct drop-foot by electrically stimulating the ankle flexor muscles during the swing phase of gait. These devices may be less bulky than AFOs, and the continued activation of the ankle flexor muscles prevents atrophy [1]. Furthermore, chronic FES use has been shown to improve mobility [5], reduce spasticity, improve cardiovascular fitness [32], and enable persons to participate in exercises that promote functional recovery [12]. The increased function and health benefits of FES make it a preferable treatment for foot drop. One of the earliest FES systems for correcting foot drop was developed by Liberson and colleagues [22]. Their approach was to place a foot switch in the shoe under the heel of a hemiplegic patient who could not dorsiflex the ankle. During walking, removal of pressure from the switch at the end of the stance phase triggered stimulation of the common peroneal (CP) nerve to dorsiflex the ankle, and prevent the foot from dropping or dragging on the ground during the swing phase. More recently, a new drop-foot stimulator Walk Aid resolved some of the problems related to the switch that controls the timing of stimulation [29]. Implanting stimulating electrodes near the motor points

of hemiplegic patient muscles can achieve greater muscle selectivity [15]. This research led to the development of the implantable system Actigait® that is now coming at the market from Neurodan A/S, Denmark, part of the Otto Bock HealthCare, Germany. The implantable stimulation systems are likely the solution in the cases where life-long use is required, but the use of surface stimulation should be performed in order to increase the recovery and to determine whether an orthosis is needed.

In summary, stimulating the CP nerve thereby inducing dorsiflexion during the swing phase of gait is an effective alternative to splint (AFO). In most cases, drop-foot stimulation was considered only as an orthosis. However, four RCTs examined drop-foot stimulation as an orthosis for gait retraining. Cozean *et al.* [8] found that FES combined with biofeedback produced better results than standard physical therapy or FES or biofeedback alone. MacDonnel *et al.* [23] found that FES combined with physiotherapy was superior to physiotherapy alone in improving ambulation scores. Similarly, Burridge *et al.* [5] found that FES combined with physiotherapy was superior to physiotherapy alone in significantly improving gait speed while reducing the energy costs. The benefit was only noticeable when the stimulator was being used, but also after the use. The suggestion is that FES that corrects drop-foot results in improvements of hemiplegic gait.

Body weight support and treadmill training

Several RCTs compared the intensive walking exercise with traditional rehabilitation treatments. These RCTs suggest somewhat conflicting evidence as to whether this intervention, in the absence of partial body weight support, offers any advantage over standard treatment. Among non-rated studies examining pre-and post-interventional changes associated with treadmill training in small numbers of hemiplegic patients, there is evidence of benefit with the majority of studies appearing to demonstrate a beneficial effect in the absence of adequate controls. The preferable technique included partial body weight support in combination with treadmill training (Fig. 2). The body weight support approach to motor recovery is appropriately summarized as ''those who want to walk can learn how to do it by exercising to walk'' [16]. The positive outcome was initially interpreted based on animal model experiments and the central pattern generator concept. Harkema *et al.* [14] and Dobkin *et al.* [10] reported that sensory input associated with normal stepping elicits locomotor behavior even

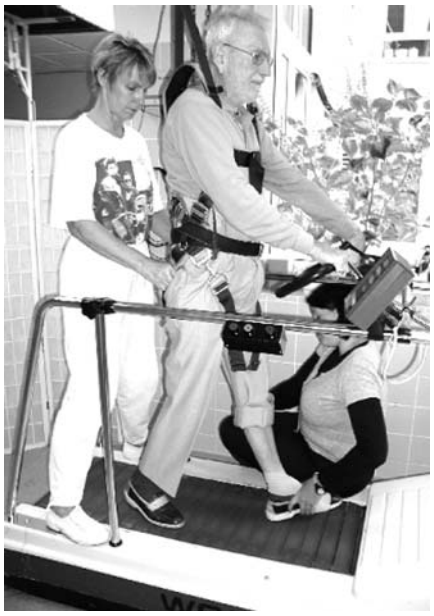

Fig. 2. Training of walking on a powered treadmill and body-weight support. Courtesy of Dr. Thierry Keller, ETHZ and Balgrist Hospital, Zurich, Switzerland

in the hemiplegic patients with a thoracic spinal cord injury. Consequently, this has led several investigators to study body weight-supported treadmill training after stroke in an attempt to optimize locomotor-related sensory input to all neural regions that are involved in walking. This strategy is thought to increase the functional independence and speed of walking. Hence, there appears to be a strong neurophysiological basis for this mode of gait retraining. On a more practical level, the body weight support attempts to provide postural support and promote coordination of the lower extremities. The decreased weight bearing, theoretically, allows more physiological movement strategies by minimizing weight-bearing demands. Confidence of hemiplegic patients becomes greater because of a reduced risk of falling while still being engaged in the task. The body weight support can be gradually withdrawn as the hemiplegic patients' posture, balance, and coordination improve. Hesse *et al.* [16] suggested that: ''Task-specific therapy can enable hemiplegic patients to practice walking repetitively, in contrast to conventional treatment in which tone-inhibiting maneuvers and gait-preparatory tasks during sitting and standing dominate. The treadmill with body weight support technique employs a modified parachute harness to substitute for balance deficiency. The rotating treadmill belt requires complex stepping movements. The harness is used to promote the vertical body position; swinging in the harness is avoided. If the hemiplegic patient assumes a flexed body

position, the point of suspension can be moved posteriorly so that the trunk is erect. When correctly positioned, the harness supports a proportion of body weight, allowing the hemiplegic patients to support the remaining weight adequately without knee collapse or excessive hip flexion during the single-stance period of the affected lower limb.''

Robot assisted walking of hemiplegic patients

As described earlier, it was demonstrated that task specific intensive exercise, in this case walking on a powered treadmill, promoted the recovery of function. However, it also was evident that better control and less physical activity of a therapist could facilitate this therapy. This directly led to the design of robots that provide repetitive life-like movement of the legs. The two best examples are the Advanced Gait Trainer® (Fig. 3) produced by the company Reha Stim, Berlin, Germany, and Locomat® (Fig. 4) produced by the company Hocoma AG in Switzerland [18]. The Advanced Gait Trainer® is a robot that moves the feet of the hemiplegic patient in a manner similar to the normal walking pattern. The robot comprises the partial body-weight support, and provides some force that controls the position of the pelvic region. The Locomat® generates the movements of the hip and knee joints alike normal walking, and the feet positions are only controlled with a spring like harnesses that prevents drop-foot. The hemiplegic patient is partially supported with a harness over the powered treadmill. In both cases the robots provide excellent assistance and allow long time exercise without the risk of a hemiplegic patient falling. The clinical studies provided sufficient evidence that the robot assisted walking lead to bigger gains compared with the conventional or treadmill assisted walking. The outcome measures that were used to support the robots employed for therapy are the speed of walking, symmetry, EMG patterns that are recorded in paretic and non-paretic limbs, spasticity, etc. There has been no large multi-center study to confirm these findings.

Fig. 3. Advanced Gait Trainer®. The robot that moves feet mimicking life-like movements. The system provides controlled body-weight support. The robot is available from Company Reha Stim, Berlin, Germany

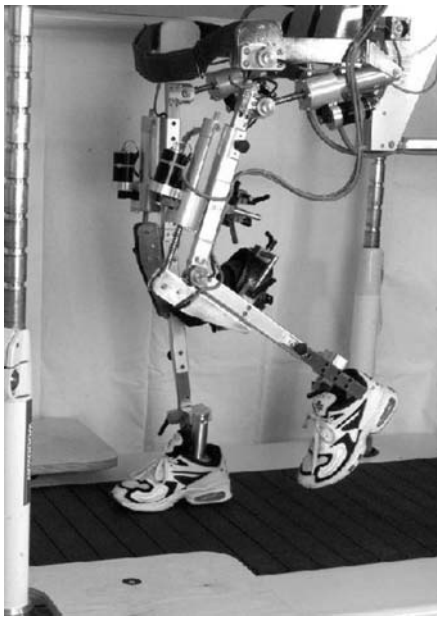

Fig. 4. LOCOMAT®. The robot that assists leg movements on the powered treadmill. The harness provides controlled body-weight support. The system is available from Hocoma AG, Switzerland

Functional electrical therapy (FET) of walking

Functional Electrical Therapy (FET) combines intensive voluntary activation of preserved sensory-motor systems and patterned multi-channel electrical stimulation of paralyzed muscles. The essential difference between FET and FES is that in FET electrical stimulation assists several gait events (stance, swing, push-off, etc.) and operates as a complex neural prosthesis. This orthotic assistance allows a hemiplegic patient to regain almost natural walking during the period that his leg is paralyzed. The added motor ability motivates a hemiplegic subject to exercise in a functional manner, i.e., to practice typical movements that were part of his/her normal daily activity before the CVA. The electrical stimulation in FET sends strong signals to the CNS that are timely superimposed to the proprioceptive and

exteroceptive sensory activity that occurs during the functional tasks. Popovic *et al.* [25] reported large improvement in functioning of acute and modest improvements in chronic hemiplegic subjects after three weeks FET applied to hand. In this RCT, they demonstrated that externally controlled activation of sensory-motor systems in synchrony with aimed movement contributed to greater recovery when compared to the conventional therapy. This result is well supported by a study of Khaslavskaya and Sinkjær [20] where they demonstrated physiological basis for the recovery.

FET of walking comprises synchronized stimulation of main muscle groups of the paretic leg during the stance and the swing phases of the gait (Fig. 5). Stanic *et al.* [28] found that multichannel electrical stimulation, given 10 to 60 minutes, 3 times per week for one month, improved the gait performance in hemiplegic subjects. Bogataj *et al.* [3] applied multichannel electrical stimulation to activate lower limb muscles of 20 chronic hemiplegic subjects. After daily treatment 5 days per week for 1 to 3 weeks, the subjects who were previously unable to walk, walked again. In the 1990s, electrical stimulation has been increasingly used to treat the lower extremity of stroke subjects. Bogataj *et al.* [4] compared two groups of stroke survivors receiving 3 weeks of electrical stimulation, preceded or followed by 3 weeks of conventional therapy. The treatment was given 5 days per week for 7 to 21 days. The results showed that more subjects were able to walk independently after electrical stimulation. However, these studies had not adopted a randomized control design: treatment period within a study was often not standardized; the studies failed to calculate the sample size; the subjects were mostly examined during the chronic stage; and the interval to therapeutic intervention after stroke varied within each study [6, 11].

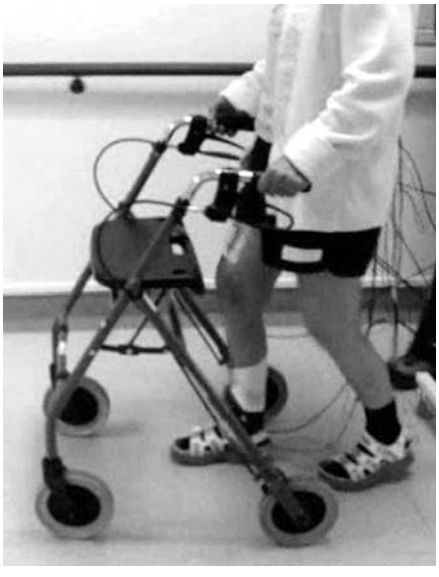

Fig. 5. FET walking with up to 4 channels of surface electrical stimulation. The therapeutic device is UNA FET multichannel programmable stimulator, Belgrade, SCG

Recently, we started the FET of walking clinical trial where patterned electrical stimulation was applied during the walking sessions [26]. The preliminary findings are that the recovery of walking, that is, the ability to walk without assistive system, is significantly better in the FET group when compared with the group of hemiplegic patients who received only conventional therapy.

Yan *et al.* [33] hypothesized that the FES-induced afferent-efferent stimulation that results in limb movements plus cutaneous and proprioceptive input during the acute stage could be important in ''reminding'' the subjects how to perform the movement properly. Therefore, they investigated whether FES combined with a standard rehabilitation (SR) program was more effective than SR given with placebo stimulation or alone in promoting the recovery of motor function and functional mobility during acute stroke. The multi-channel stimulation in the study of Yan with collaborators was applied to hemiplegic patients in laying position. 15 sessions of FES, given 30 minutes per session plus conventional therapy, 5 days per week, improved motor recovery and functional mobility in acute stroke subjects more than placebo stimulation and conventional therapy, or conventional therapy only. The significant recovery after FET in acute hemiplegic subjects suggests that synchronizing spontaneous and therapy induced recovery is instrumental for reaching faster the higher level of functioning. An explanation of this phenomenon is that the plasticity of central nervous system is greater shortly after the lesion compared with the ability to adapt in the chronic phase of disability. A conclusive result from this review is that the FET should be applied in acute hemiplegic patients immediately after they can stand with hand supports. The FET could be initiated even in the laying position [33].

The most likely physiological explanation of the effects is the cortical reorganization evoked by the FET. Hamdy *et al.* [13] reported that for at least 30 minutes after pharyngeal stimulation, the motor cortex excitability and the area of representation for the pharynx increased while the esophagus representation decreased, without parallel changes in the excitability of brainstem-mediated reflexes. The excitability of corticospinal pro-

jections to antagonist muscles was studied in sixteen healthy subjects and one patient with a focal brain lesion [2]. Their results suggest that activation of the median nerve can suppress the excitability of cortical areas controlling the antagonist forearm extensor muscles acting on the hand. Ridding *et al.* [27] performed a study to determine whether prolonged, repetitive mixed nerve stimulation of the ulnar nerve leads to a change in excitability of primary motor cortex in normal human subjects. They showed that the area of the motor evoked potential (MEP) evoked in the ulnar, but not the median-innervated muscles, was increased after prolonged ulnar nerve stimulation. Control experiments employing electrical stimulation provided no evidence for a spinal origin for the excitability changes. These results demonstrate that in human subjects the excitability of the cortical projection to hand muscles can be altered in a manner determined by the peripheral stimulus applied. Khaslavskaya *et al.* [19] and Khaslavskaya and Sinkjær [20] studied the effects of repetitive electrical stimulation of the common peroneal nerve and its association with changes in the motor response of the *Tibialis Anterior m.* elicited by focal transcranial magnetic stimulation (TMS). They showed that short term nerve repetitive electrical stimulation in lower extremities of healthy human subjects could lead to a long-term increase in the contralateral MEP. The results allow speculating that it is possible to use repetitive electrical stimulation in the rehabilitation of hemiplegic patients with muscle weakness and spasticity.

Figure 6 illustrates the hypothetic trends in the recovery of functioning when hemiplegic patient is exposed to no, intensive, and functional electrical therapy augmented treatments in addition to conventional therapy. In all cases, the recovery of function is substantial within the first few months after CVA. The plateau is typically reached at about 6 months [24]. The intensive therapy (robot induced movement, treadmill training, strengthening, etc.) lead to better recovery of function. FET is likely to promote recovery because it operates as an orthosis during the period that the hemiplegic patient is not able to walk. This orthosis provides the substrate for the engagement of preserved sensory-motor function, prevention of disuse atrophy and development of compensatory mechanisms, and strong timed training of the CNS structures.

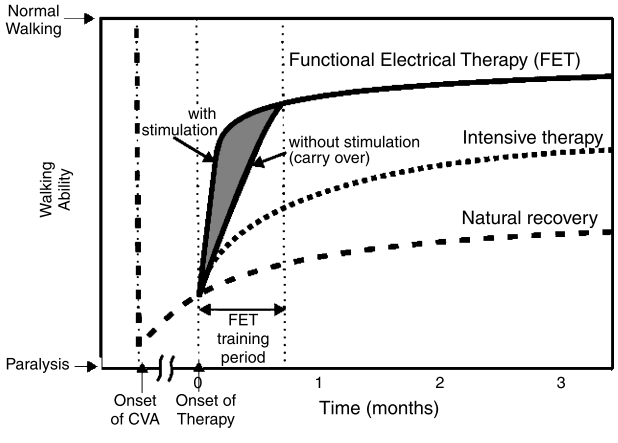

Fig. 6. The hypothetic recovery of walking abilities due to neuromodulation induced by task-oriented intensive exercise

In summary (30):

- There is moderate evidence that strength training improves the efficacy of gait post-stroke
- There is moderate evidence that the ''drop-foot'' FES, and gait retraining results in improvements in hemiplegic gait
- There is conflicting evidence that treadmill training alone (without partial weight support) offers some advantage over conventional therapy
- There is conflicting evidence that partial body weight support results in improved walking and motor recovery when compared with conventional therapy, but not when compared with aggressive bracing assisted walking
- There is limited evidence that splinting of the foot alone improves various parameters of gait in hemiplegic strokes
- There is moderate evidence that ankle foot orthoses combined with posterior tibial nerve deinnervation improves the gait outcomes in hemiplegic strokes
- There is limited evidence that robot assisted walking promotes the recovery better than treadmill walking and conventional therapy
- There is moderate evidence that FET in the acute phase promotes significantly the recovery of walking compared with the conventional modalities of treatment [26, 33].

Overall, there is a need for well-designed large-scale multi center clinical trials to compare the effects of treatments of walking with the same inclusion criteria and the same outcome measures.

Acknowledgment

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FES cycling

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Summary

Spinal cord injury (SCI) leads to a partial or complete disruption of motor, sensory, and autonomic nerve pathways below the level of the lesion. In paraplegic patients, functional electrical stimulation (FES) was originally widely considered as a means to restore walking function but this was proved technically very difficult because of the numerous degrees of freedom involved in walking. FES cycling was developed for people with SCI and has the advantages that cycling can be maintained for reasonably long periods in trained muscles and the risk of falls is low. In the article, we review research findings relevant to the successful application of FES cycling including the effects on muscle size, strength and function, and the cardiovascular and bone changes. We also describe important practical considerations in FES cycling regarding the application of surface electrodes, training and setting up the stimulator limitations, implanted stimulators and FES cycling including FES cycling in groups and other FES exercises such as FES rowing.

Keywords: Neuromodulation; functional electrical stimulation; FES; cycling; rehabilitation.

Introduction

Spinal cord injury and FES

There is overwhelming evidence that exercise is beneficial to health in many respects, ranging from physical fitness (e.g. a decreased risk of heart disease and stroke) to a positive sense of well-being (e.g. mood and sense of esteem involving the perception of body image). This also applies to people who have had a spinal cord injury (SCI), but for them undertaking physical exercise is much more complicated because of the loss of voluntary activity.

A spinal cord injury leads to a partial or complete disruption of motor, sensory and autonomic nerve pathways below the level of the lesion. Because muscle function is dependant on its nerve supply, there is some degree of permanent paralysis that rapidly leads to adverse changes in muscle size and composition. Due to the ensuing lack of whole-body exercise, there is reduced cardiovascular fitness, an increased susceptibility to pressure sores and diabetes with poor tissue healing. Prolonged wheelchair use removes the normal mechanical stress of standing and locomotion on leg bones, resulting in osteoporosis, and an increased risk of bone fractures. The changes in body shape and image, along with the psychological effects of physical inactivity, predispose to anxiety and depression.

There is considerable interest in the use of electrical stimulation of the paralysed muscles of SCI people. This can be applied with minimal equipment to separate muscle groups for maintenance of their size and strength, for example with the subject sitting or lying. However used in this way, the amount of stimulation has usually been insufficient to maintain or improve health.

In paraplegics patients, functional electrical stimulation (FES) was originally widely considered as a means to restore walking function. Unfortunately, this is technically very difficult because of the numbers of degrees of freedom that need to be controlled in the legs, the variability of the muscle responses to stimulation, spasticity and spasms, the number of electrodes required and the need to coordinate the legs with the motion of the neurologically-intact upper body. A FES walking system that is attractive to many people with SCI has yet to be developed. The emphasis in research has therefore shifted and FES is probably now seen primarily as a therapeutic tool to counteract the deleterious effects of SCI.

Petrofsky and Phillips [23] initially developed FES cycling for people with a SCI. This has the advantages that cycling can be maintained for reasonably long periods in trained muscles and the risk of falls is relatively low. Therefore, it offers a practicable way to achieve the

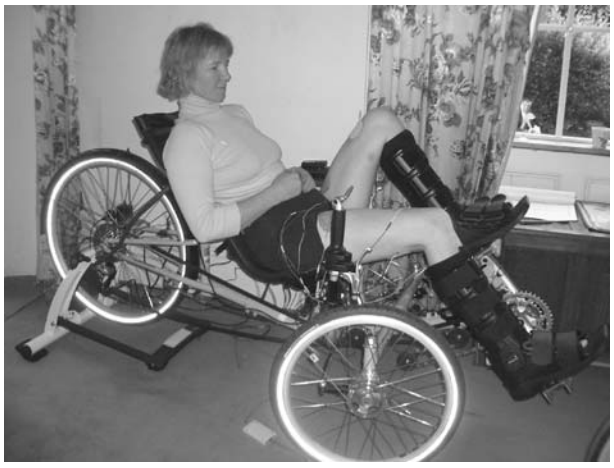

Fig. 1. FES exercise at home with tricycle on friction roller ("*trainer*"). The ankle orthoses, throttle, and electrodes on *quadriceps* and hamstring muscles can be seen. The tricycle was designed for mobile use and has standard gears and brakes. Transfer from a wheelchair is not difficult because the seats are at similar height and an upstanding handle can be temporally detached from the handle bar

health-related benefits of exercise and increase muscle bulk. A further benefit is that it offers the possibility of recreational, social exercise outside the home environment. Electrodes are placed over the target muscle groups: always over the extensors and flexors of the knee (quadriceps and hamstrings), and sometimes over some of the hip extensors (gluteal muscles), the plantarflexors, and the dorsiflexors of the ankle. The electrodes are usually large enough to cover most of the width of the muscles, to recruit as much as possible, and this means that bi-articular muscles, *rectus femoris* and *gastrocnemius*, are stimulated with the other muscles of *quadriceps* and *triceps surae* respectively.

A FES exercise tricycle is shown in Fig. 1. The cyclist sits on a wide seat that supports the hips and the trunk. Their lower legs are strapped into ankle orthoses that are themselves joined to the pedals. The orthoses are stiff and oppose lateral movement of the knees. This lateral restraint and the use of angular adjustment on the orthoses, constrain the legs to move properly despite the absence of motor control of the muscles except for the flexion-extensions motion of cycling. The aim is to produce strong pedalling movements without damaging the joints of the legs. Each muscle group is stimulated for a particular range of crank angle to turn the pedals, a shaft encoder on the crank shaft giving the stimulator a continuous measurement of the angle. Perkins *et al.* [21] found that power output can be improved if the ranges of angle for all the channels are moved forward as the rotation gets faster to allow for the response time of the muscles. The stimulation intensity is controlled by a throttle on the steering handle, thus the timing is automatic but the muscle output is controlled by the cyclist (as in a motor bike).

Effects of SCI

This section will review the physiological changes, particularly those in muscle and bone, that are associated with an SCI and also the effects of electrical stimulation and FES cycling. Referencing is limited and more recent publications are generally used through which earlier work can be accessed. The thesis of Gerrits *et al.* [12] forms a comprehensive review and the book by *Jones et al.* [17] is recommended for information on muscle structure and function in health and disease.

Muscle composition

Normal skeletal muscle contains a spectrum of fibre types ranging from the fatigue resistant slow oxidative (type I) to fast oxidative and glycolytic (IIa) and highly fatigable fast glycolitic (IIx). The relative proportion of fibre types varies between individual muscles. The human quadriceps muscle is probably the most studied and healthy able-bodied people have approximately an even distribution of type I and II fibres (range 40–60%). Following an SCI the quadriceps convert to being predominantly type II fibres (Fig. 2) [2, 26]. These fibres seem to

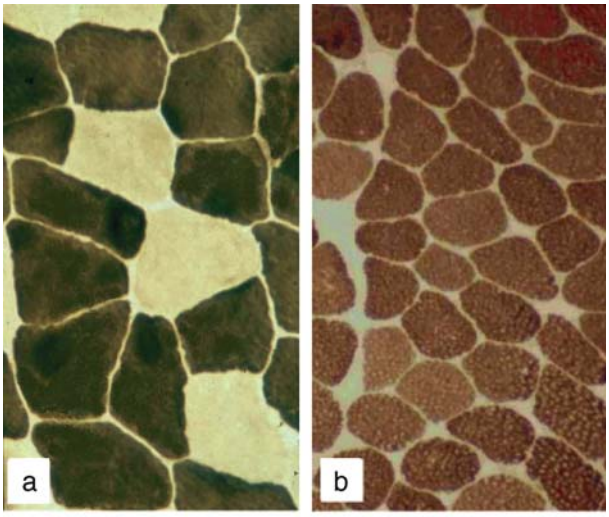

Fig. 2. Transverse section of the quadriceps femoris muscle from (a) normal healthy and (b) SCI subjects at the same magnification. The SCI subject shows smaller atrophied fibres that are exclusively type II fibres (stained dark). From Jones, Round and de Haan (with permission)

be the default setting and the presence of type I fibres is dependant on a normal pattern of activity in the motor nerves. This is lost in the paralysed muscles below the level of an SCI. Type II fibres are more fatigable and therefore the muscles of SCI people fatigue much more rapidly than those of able-bodied people [3, 10]. The substantial reduction in the amount and intensity of muscular and neural activity results in disuse atrophy and therefore affected muscles become smaller and weaker [4, 28] very soon after injury [2]. Many SCI people suffer from involuntary muscle spasms that can adversely affect activities such as transfers and sleeping. One might suppose that these would have the benefit of reducing the changes in muscle composition and bulk, but they appear to occur irrespective of whether or not spasms are a major feature for an individual.

Muscle size, strength and function

The combination of decreased muscle size and the fibre type conversion has a number of effects. The reduced muscle bulk is often a source of dissatisfaction with body image that affects psychological health. It also means that the muscles are weaker so that any activity, whether voluntary or electrically stimulated, involves working muscles at a relatively high proportion of their maximum and therefore they fatigue more rapidly than the muscles of an able-bodied person performing at the same absolute intensity. This is compounded by the loss of fatigue resistant type I fibres. Low muscle mass results in increased tissue pressures in areas susceptible to pressure sores [20] such as the buttocks. This risk is exacerbated by the vascular changes (discussed below) and the prolonged sitting periods of wheelchair users. In able-bodied people, an increased tissue pressure and the build up of metabolites become progressively uncomfortable and cause body re-positioning thus avoiding tissue damage. After SCI, these sensory warning signals are absent and the average onset of serious pressure sores is three years after an SCI. These may become infected and life threatening and are a common cause of hospitalisation for SCI people. The seriousness of developing pressure sores in exacerbated by poor tissue healing (Basson and Burney, 1982).

In addition to the quantitative changes, there are also qualitative changes that affect muscle contractile properties. Muscles below the level of the lesion are not only weak but also highly fatigable, presumably due to the change in fibre type, reduction in oxidative metabolism [19, 25] and perhaps to the peripheral circulatory changes mentioned below. These changes are common to all paralysed muscles, although the rate of change after SCI is greatest in the large postural muscles of the leg [14, 27]. The speed of contraction and relaxation also changes and, in the majority of muscles, it increases [10]. The contractile properties show a significant shift toward normal values after as little as 6 weeks of FES cycling (30 min, three times weekly) although increases in size and strength do not occur until al least two weeks later [12].

Human movement is dependant more on power output rather isometric strength although traditionally the latter is measured in muscle studies. The components of power, force and mechanical speed, are both affected by SCI; decreasing the former and increasing the latter. The influence of strength predominates and people with a SCI generate very low levels of power with FES. Even after prolonged FES cycle training, the power output achieved is substantially less than that achieved by able-bodied people (generally in excess of 200 W) and may be insufficient for outdoor cycling on anything other than smooth, level ground. Irrespective of the intensity and duration of the FES cycling, the highest maximal power outputs reported are not more than 55 W and generally in the order of 20 W [6]. A large individual variation in the response to FES cycling has frequently been reported; the reasons for this are not understood but are not obviously related to the subjects' age or the site or duration of the spinal injury. The engineering aspects of the FES tricycling should be optimised. Pedalling speed, the timing of the stimulation to the muscles, the envelope of the stimulus pulse train, and mechanical efficiency of the tricycles may all yield some improvement in power output. However, in our view, most of the difference in power output between the able-bodied and the spinal cord-injured person using FES are essentially to do with the muscle. Many possible explanations exist, including the abnormal muscle fibre distribution and atrophy, the low density of capillaries, poor vascular perfusion leading to metabolic fatigue, synchronous activation of the motor units in comparison to the asynchronous firing that occurs with voluntary activity and the loss of sympathetic control.

Another explanation that has been proposed is that electrical stimulation recruits muscle fibres in the opposite order to that which occurs with voluntary exercise. Normally, the fatigue resistant type I motor units are recruited first and the highly fatigable type IIx fibres are activated only when high forces are required. External electrical stimulation activates the type IIx fibres first

in *normal* muscles with mixed fibres. However, this is an unlikely explanation after SCI because all the motor units soon become fast (type II) after injury and if they convert back with training, will not necessarily convert back to their original types. These various explanations for low power output are largely speculative and their importance and relative contribution is unknown. An interesting finding is that when healthy able-bodied people perform FES cycling after being temporarily paralysed by an epidural anaesthetic, they produce approximately half the power output achieved at the same oxygen consumption and heart rate with voluntary effort [18].

Cardiovascular changes

SCI affects both the central and peripheral circulatory systems. Depending on the level of the lesion, decreased cardiopulmonary fitness [5] and loss of vasomotor regulation may occur. Poor cardiopulmonary fitness is particularly important, as it is associated with an increased risk of cardiovascular disease. Arterial diameter, capillarisation and limb blood flow are reduced below the lesion level, presumably due to lower activity levels and metabolic demand [11]. These probably also contribute to high rates of fatigue seen in the muscle of SCI people. Increased physical activity, whether by voluntary or electrically stimulated exercise, can reverse these changes and improve blood flow in the affected tissue [13]. Short-term FES cycle training brings about significant increases in peak heart rate and cardiac output as well as reducing sub-maximal heart rate.

Bone changes

Lower body bone strength decreases after an SCI because of the loss of the mechanical stimulus provided by weight bearing and impact forces during locomotion changes in muscle activity and perhaps those in neuronal activity and hormone levels. This leads to osteoporosis [9] and an increased risk of bone fractures [15]. The rate of decline appears to differ between individual bones and with the type of bone [8]. In the femur, bone mineral density (BMD) declines by approximately 20% in the first year after SCI and for the next five years at approximately 5% each year. Thereafter the rate of BMD decline is much less. Decreases of BMD in trabecular bone are greater than in cortical bone and greater in bones further below the level of the spinal lesion and, therefore, are greater in the distal femur and tibia, rather than in the proximal femur or spine. Decreased BMD occurs in paralysed limbs but may increase in the upper limbs of paraplegics, presumably due to the increased use of the arms for movement and propulsion. As BMD declines with age and particularly after the menopause, post-menopausal women with an SCI are at particular risk of osteoporosis.

The effect of FES cycling on BMD is unclear [8]. Some studies report no change after 3–12 months of FES training while others find either a decreased rate of decline or even an increase. There are a number of possible reasons for at least part of the explanation for the conflicting results: BMD has been measured at different sites in different bones; people with very different length of time since SCI and therefore very different initial BMD values have been studied, and they have been able to generate only very low power outputs. There is a suggestion that BMD is more susceptible to change in the first couple of years after SCI and that those who achieve higher forces and power output with FES are more likely to show an increased BMD or at least a decrease in the rate of decline. With FES the changes in muscle strength and power output occur much more rapidly than any increase in BMD and a person with strong muscles but weak bones has an increased risk of a spontaneous fracture, even in the absence of trauma. At present the absolute forces that are safe for a given bone strength are unknown and any force limits are essentially arbitrary. Further research should enable the development of much clearer guidelines about the maximal forces that are safe to be generated with a known BMD.

Practical considerations

Surface electrodes

Applying and removing surface electrodes is time-consuming. Paraplegics with mid-thoracic injuries generally use self-adhesive electrodes and it can take up to an hour to attach sixteen electrodes (for bilateral stimulation of four muscle groups), connect the cables and transfer to the tricycle. These actions must be reversed at the end of the exercise. Thus, one hour of cycling exercise may take 2.5 hours. ‘‘Electrode trousers’’ with windows for the electrodes are commercially available, but users generally do not find them easy to either put on or take off. If, by improved design and materials, more effective electrode garments were available that reduced the overall time needed for exercising, then FES exercise

would become more practicable and attractive to many people. Some users suffer from skin reddening or blistering even when no current is passed through the stimulating electrodes, even those that are claimed to be ''hypo-allergenic''. It is not known at present whether sensitive users can always avoid allergic reactions by substitution of other types of electrode. Three out of five subjects in our current study have developed reactions to one type of electrode within a year of cycling for 5 hours per week.

Training and setting up the stimulator

We apply the following criteria before muscle training for FES exercise. The person must:

- be able to transfer from wheelchair to tricycle without assistance;
- have sufficient range of motion of the leg joints;
- not have any spasms that continue long after transfer;
- have little spasticity.

In practice what this means is that the candidates are asked to transfer themselves to a tricycle; the feet are inserted into the orthoses; and the pedals are then slowly turned by the examiner who can feel and observe forces from the joints or muscles. The distance of the crank shaft from the hips should already have been correctly adjusted for the candidate. If the candidate has poor range of motion, short cranks may be used. It may be dangerous to strengthen the muscles of those with much spasm or spasticity because fractures may result.

Those who are suitable should then undergo a period of progressive muscle training in which the duration per day and the mechanical resistance is gradually increased. This training schedule should be supervised. When the strength and endurance of the muscles are enough to justify the tricycle or ergometer, cycle training can begin. Someone with adequate experience should observe the recruitment of the muscles in response to stimulation with the electrodes of the sizes that will be used. It is important to identify the *threshold* for muscle contraction and the *maximal* at which either there is no further increase in the force of the muscles one want to recruit or there is contraction of adjacent non-synergistic muscles, such as the adductors of the hips. It is best to make these observations while the subject is lying down, not constrained by being on the tricycle. For all the muscle groups in use, these levels should be set as parameters in the stimulation program.

Where to do it

Petrofsky *et al.* described an ''outdoor bicycle [sic] for exercise in paraplegics and quadriplegics'' in 1983 [24]. Subsequently he, with Glaser and others carried out many scientific studies of FES cycling on ergometers, such as the *Ergys* and *StimMaster* that have been commercially available. These machines are expensive and

Fig. 3. Playing the *Cushion Game*, 2- or 3-a-side. A cushion is used instead of a ball

Fig. 4. The *Cushion Game*, can be fast and exciting to watch even though none of these paraplegics can produce more than about 30 W after their training. The important point is that they enjoyed playing, and could continue for over an hour

their use outside scientific studies seems to have been mainly restricted to use within rehabilitation clinics. We suggest that this is not appropriate for long-term frequent use for body maintenance and that not enough importance has been attached to the fact that stationary cycling performed indoors for long periods of time is boring and requires exceptionally highly motivated subjects if it is to be incorporated into the long term life style of an individual. Perhaps Janssen *et al.* [16] recognised this when they wrote: ''It should be remembered that participation in such exercise must be part one's lifestyle if optimal beneficial effects are to be realised and maintained''. We suggest that if the people with SCI are to maintain long-term FES cycling, it should have the possibility to be a sporting or recreational activity that can be outdoors where the ground is relatively level, or for sporting activities such as races and games in sports halls. We recently gathered eight complete thoracic paraplegics, who had been doing cycle training at home, to a sports day at which there were relay and slalom races, and later a novel team game (Figs. 3 and 4). The competitors and audience evidently enjoyed the new sports that gave an added incentive to continuing the home training regimes. The ability to participate in recreational outdoor cycling is an important goal for many and after sufficient training is feasible on smooth and level surfaces.

Limitations

In our experience, most paraplegics can be trained to achieve an endurance capacity that enables them to pedal continuously for at least an hour. The current obstacle to performing outdoor recreational FES cycling is the low peak power (20–30 W), which is insufficient for hill-climbing or crossing rough surfaces. What limits this power is, therefore, of great interest and should be the subject of future research to investigate what improvements can significantly increase power output. Until then, legs-only cycling will probably be restricted to exercise indoors or on smooth and level outdoor surfaces. Alternatively, vehicles in which the arms can supplement the legs as necessary, such as the BerkelBike (http://www.berkelbike.nl/), or tandems with one able-bodied cyclist, would bypass the current power limitations. Some people cannot accommodate a mobile recumbent tricycle in their homes because of space restrictions; about 2×2 m is required including space for the wheelchair during transfers. For those who would like to exercise at home but have no interest in mobile

cycling, a small ergometer, perhaps placed in front of a television or computer, may be preferred.

Implanted stimulators

Even if improved electrode garment design reduces the time required before and after the actual exercise period, the time required may still be a disincentive to busy SCI people and limit frequent and regular exercise. Allergic reactions of the skin are another complication of prolonged use of surface electrodes. These disadvantages of surface electrodes would be avoided by use of surgically implanted stimulators that are started simply by switching on the signal transmitter. A major issue is the site of the implanted electrodes, considering the functional performance, cost, risks, and reliability. This is a complicated optimisation but the placement of intrathecal electrodes on the lumbar and sacral nerve roots is an attractive possibility [7]. The long-term reliability of electrodes at this site is established; all the electrodes can be placed in one surgical field and bladder and bowel control can be obtained with the same implant. Having had such an implant, one volunteer had strong responses from 11 of her 12 stimulated roots and she demonstrated powerful cycling and good endurance performance (Fig. 5). Perkins *et al.* [22] have described the method. We are currently preparing for a trial of a stimulator implant – the Sacro-Lumbar Anterior Root Stimulator (SLARSI) –, which is aimed as functional cycling and bladder/bowel control using the methods of the Finetech-Brindley SARSI implant (www.finetech-medical.co.uk).

Fig. 5. Paraplegic cycling with implanted *Lumbar Anterior Root Stimulator Implant* (LARSI)

Other groups of patients

Among people with SCIs, those with thoracic lesions have the advantage of enough upper body strength for transfers to and from a wheelchair, some voluntary activity of postural trunk muscles and enough dexterity to accurately position the electrodes. Their upper-body function also allows them to play wheelchair sports for exercise. Tetraplegics have none of these advantages and so for them, FES exercise is more valuable and yet more difficult to achieve. They will need tricycles that are more adapted to support their trunks and probably adapted controls for steering, braking and gear changing. An implanted stimulator will be more easily justified, given their very limited manual abilities. As far as we know, mobile FES tricycling has not been attempted with complete tetraplegics since Petrofsky *et al.* [24]. Patients with incomplete spinal injuries may also benefit from FES cycling. In their case, it appears that FES may cause some motor re-learning so that they become less disabled for daily activities as a result [6]. Further research is required on the carry-over effect from electrically stimulated to voluntary muscle activity.

FES rowing

More recently, FES has been used to generate a rowing action on static machines [29]. This produces higher power outputs and cardiovascular responses than are achieved during FES cycling. In rowing, the trunk and arm muscles make a substantial contribution to the power generated, but none to FES cycling unless people use their hands to push on the knees. The greater musculature involved is beneficial in terms of cardiovascular improvements, but may be at the expense of increased wear and tear on the shoulder joints that often cause problems to long-term wheelchair users. At present FES rowing is exclusively an indoor activity and thus offers less social and recreational potential than FES cycling.

Acknowledgements

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Reconstruction of upper limb motor function using functional electrical stimulation (FES)

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Summary

Functional electrical stimulation (FES) techniques progress by adopting the developments in computers and engineering, but complete functional reconstruction is not yet possible to be achieved. The attachment of the devices to the body can be complex, and training to handle FES is not easy. FES systems are expensive and their coverage by medical insurance is limited with the exception of a few systems. Hence, recognition of FES by the medical community is limited and as a result, it is not a common therapy. However, FES is the main method available for reconstruction of motor function, at present. The improvement in activities of daily living (ADL) of patients using FES may not only improve the patient's quality of life (QOL) but also reduce the burden to persons who look after them, and hence, secure a valuable work force. The medical insurance should support the use of FES and reduce the patients' financial burden. Studies and developments based on a close collaboration of users (patients and care-givers), persons involved in therapy (doctors and nurses), and manufactures (engineers and technicians) are necessary. In addition to FES, other methods such as therapeutic electrical stimulation (TES) for prevention of atrophy and spasms of paralytic limbs show the therapeutic potential of neuromodulation.

Keywords: Neuromodulation; functional electrical stimulation; FES; upper limb; monoparesis.

Introduction

Motor function disorder after spinal cord injury or cerebral stroke causes serious damage to a patient's daily and social life. In many cases, this requires another person to look after the patient something that represents a heavy burden for most families. Such patients need to undergo rehabilitation to train their residual function and improve their activities of daily living (ADL) but unfortunately, the benefits can be limited. Neuroregeneration has been investigated, but its clinical application is limited at present. Reinstitution of motor function by inducing contraction of paralytic muscles by functional electrical stimulation (FES) has been investigated extensively. Liberson *et al.* performed FES in 1961 to improve gait by stimulating the peroneal nerve in a patient with foot drop and cerebral stroke-associated hemiplegia [6]. This therapy is expected to make significant progress based on the recent developments in computers and engineering and the cooperation with biomedical engineers. In this report, we will describe the concept of FES and its various fields and indications, the therapeutic electrical stimulation (TES), and the FreeHand system, which is a complete implanted type of FES for reconstruction of upper limb motor function.

Concepts and fields of FES

FES is defined as 'reconstruction of biological function lost due to diseases and disorders by controlled electrical stimulation'. FES covers a wide variety of fields (Fig. 1). However, as a brief introduction to the main application of FES, i.e. motor reconstruction, the other most important applications are described below.

Visual FES

Dobelle attached an electrode to the optic area of the cerebral cortex, and, through electrical stimulation, the patient sensed pictures taken by a video camera attached to the glasses. Its effect is debatable, but the bionic eye research attracted attention. Studies of electrical stimulation of the optic nerve and retina have also been performed [1].

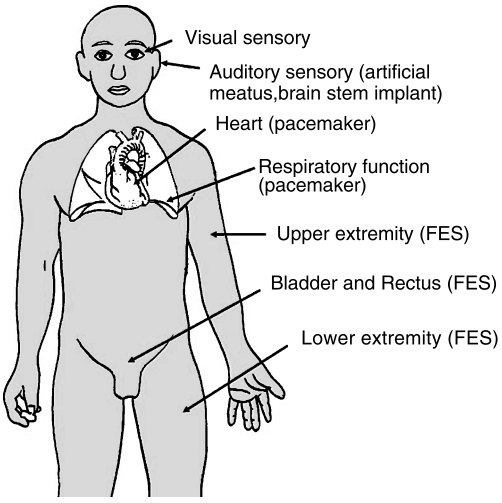

Fig. 1. Applications of FES

Auditory FES

In auditory FES, artificial inner ears and auditory brainstem implants are available. The electrode of an artificial inner ear is implanted into the cochlea, and the cochlea nerve is electrically stimulated. Artificial inner ears are indicated for deafness associated with inner ear disorder. The implantation of an auditory brainstem implant involves the insertion of the electrode at a site above the cochlear nuclei. Since the acoustic nerve transmits information to secondary neurons at the brainstem cochlear nuclei, auditory sensation is reconstructed by stimulation of this region. The indication is deafness associated with bilateral acoustic nerve injury; most cases are neurofibromatosis type 2 (NF2) that develop acoustic nerve tumor [2].

Visceral FES

With respect to heart function, cardiac pacemakers are very well established. In dilated cardiomyopathy, cardiomyoplasty may be indicated; the latissumus dorsi muscle is sutured around the heart and electrically stimulated to assist cardiac pump function.

With respect to respiratory problems, breathing pacemakers that electrically stimulate the phrenic nerve are available. Upper cervical spinal injury and central hypoventilation syndrome are the main indications; unlike cardiac pacemakers, breathing pacemakers are very expensive; in Japan, they are not covered by medical insurance, and therefore, not widely used. Respiration induced by breathing pacemakers is similar to physiological respiration, unlike the respiration that is supported by a respirator. Furthermore, breathing pacemakers are useful with regard to the possibility of weaning a patient from the respirator [3, 7].

In vesicorectal FES, electrical stimulation is applied for spinal cord injury-associated neurogenic bladder. Electrical stimulation through a surface electrode attached to the sacral region is generally performed, and its efficacy has been clinically established. Takaoka's group at Case Western Reserve University developed the Vocare System, a complete implanted electrical stimulation system, in which the electrode is attached to an epidural site after intradural cutting of the dorsal root. This system has been approved by the FDA and applied to more than 100 cases [4]. Briefly, laminectomy of T12 and L1 is performed to reach the cone. The dorsal roots S2–S5 are cut intradurally to prevent reflex incontinence (reflex vesical contraction) and maintain a vesical capacity. After this, the electrodes are epidurally attached to S2 and S3. A receiver is implanted under the lateral abdominal skin. Intermittent electrical stimulation for 3 seconds followed by a 6-second interval is applied to the nerves. The urinary bladder and sphincter muscle of the urethra contract during stimulation, but only the sphincter muscle of the urethra relaxes during the interval and urination occurs. Patients are enabled to urinate voluntarily, reflex incontinence is resolved, and the residual urinary volume decreases, thus reducing the risk of urinary tract infection.

Motor FES

Reconstruction of motor function by electrical stimulation is the best-known field of FES. There are many commercialized products. Motor FES is roughly divided into FES for upper limb motor function and FES for lower limb motor function.

In upper limb motor FES, HANDMASTER developed by Nathan and Triolo in Israel [10] and Bionic Glove developed by Prochaska *et al.* at Alberta University in Canada [10] are available. These aim at reconstruction of grasping motion using a surface electrode.

In Japan, the Tohoku University group developed a system that uses a skin-perforating implant electrode. This is a 30-channel system, and is employed for advanced medical treatment. Praxis system being developed by Davis *et al.* and FreeHand system developed by Peckham *et al.* [8] of Case Western Reserve University in the USA are complete implant systems. Praxis system aims at simultaneous reconstruction of upper and lower limb motor function and vesical urination. FreeHand system has 8-channel electrodes and recon-

structs 2 types of grasping motion [5]. Lower limb motor FES is investigated for standing up and walking. The main stream application is hybrid FES consisting of a combination of brace and FES. In Japan, Shimada's group at Akita University added FES to the original Walkabout and its modified version, Primewalk, and is actively applying the systems to clinical cases.

Electrodes of FES

Paralysis of the limbs due to spinal cord injury and cerebrovascular disorder is associated with impairment of the brain and spinal cord i.e. impairment of upper motor neurons. When peripheral lower motor neurons maintain function and react to electrical stimulation, muscle contraction can be induced. Utilizing this transneural induction of muscle contraction, stimulations programmed for individual necessary muscle groups are added to reconstruct motor function with coordinated muscle contraction; this is called FES (Fig. 2).

There are 3 types of FES electrodes; surface electrodes, skin-perforating implant electrodes, and complete implant electrodes.

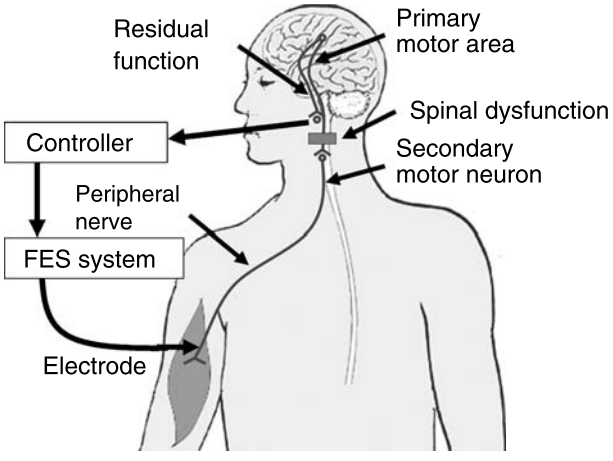

Fig. 2. Schematic representation of FES application in limb paralysis

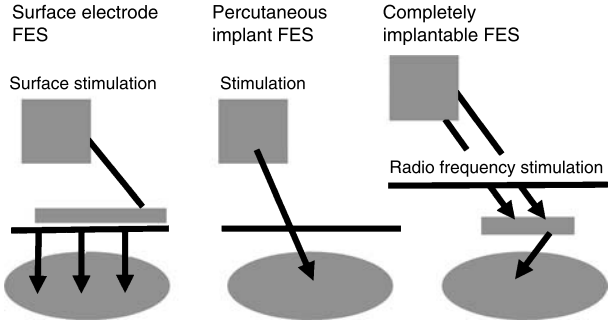

Fig. 3. Schematic representation of the types of FES electrodes

In the surface electrode system, electrode pads are applied to the body surface for stimulation. In another method, electrodes are integrated into the brace, and the brace is attached. Advantages of surface electrodes are the simplicity and non-invasiveness of attachment. Disadvantages are the low selectivity because only relatively large surface muscles are stimulated, and the low accuracy of stimulation because the stimulation changes when the attached electrode gets displaced, which may give unpleasant feelings on the skin.

In the skin-perforating implant electrode system, the electrode is percutaneously inserted into the motor point of the muscle, and connected to an external stimulator. Selective stimulation of deep muscles is possible. The electrode does not get displaced from the inserted site; hence, it is possible to stabilize the stimulation compared to the surface electrodes. As a disadvantage, there is a risk of infection through the insertion site because the lead of the electrode perforates the skin. Users are quite anxious about bathing and disinfection of the insertion site.

In the completely implanted electrode system, electrodes, lead and stimulator are completely implanted in the body, and signals for stimulation are sent externally through an antenna. This system is waterproof with minimal risk of infection and has the advantage that there is no traffic between the inside and outside of the body. Many problems remain to be solved. The implantation of a FES system causes surgical stress, the system is very expensive, and the number of channels is limited compared to the skin-perforating system; nevertheless, this is the best method available at present.

Indications of FES and therapeutic electrical stimulation (TES)

The indication of FES is impairment of upper motor neurons that is spinal cord injury and cerebrovascular disorder. Peripheral neuropathy, which is impairment of lower motor neurons, is not an indication. Necessary pre-conditions are the absence of contractures or ossifications of joints, ability of obtaining sufficient muscle strength by electrical stimulation, and normal higher function that can be trained.

In reconstruction of upper limb motor function, the quadriplegia due to a C4–C7 spinal injury and the hemiplegia due to cerebrovascular disorder represent indications for the method. However, in spinal cord injury, anterior horn cells are injured at the injured level, and denervation occurs in lower motor neurons with the

damaged anterior horn cells, loosing their responsivity to electrical stimulation. This event is called ''dead band''. Since denervation may interfere with FES-induced reconstruction of motor function, it is essential to investigate dead bands before the procedure. When dead bands are localized in one region, reconstruction of motor function by combination of FES and tendon transfer is possible.

When denervation has not occurred but sufficient muscle strength cannot be obtained because of disuse muscle atrophy, TES should be tried. TES is performed to prevent and improve disuse atrophy of paralytic muscle associated with upper motor neuron impairment and inhibit spasm of antagonists. Stimulation of the motor branch controlling the muscle increases the muscular contractile force and muscular volume due to an efferent effect; the muscle strength and range of motion also increase. Afferent effects produced by stimulation of the sensory branches from the muscle spindle, tendon organs, and fascia inhibit the spasm of the antagonists through reciprocal inhibition. These effects are useful as part of the training before introduction of FES; they may also increase the resistance to muscle fatigue and to rehabilitation for paralysis.

FreeHand system

The FreeHand system is a compete implant FES system for the reconstruction of upper limb motor function developed by Peckham *et al.* at Case Western Reserve University in the USA [5, 8]; this was approved by the Food and Drug Administration (FDA) of the USA in August 1997. It is equipped with epimysial electrodes, and reconstructs 2 types of grasping motion. The indication is cervical spinal injury of C5 and C6. Various applications of the system have been investigated, such as

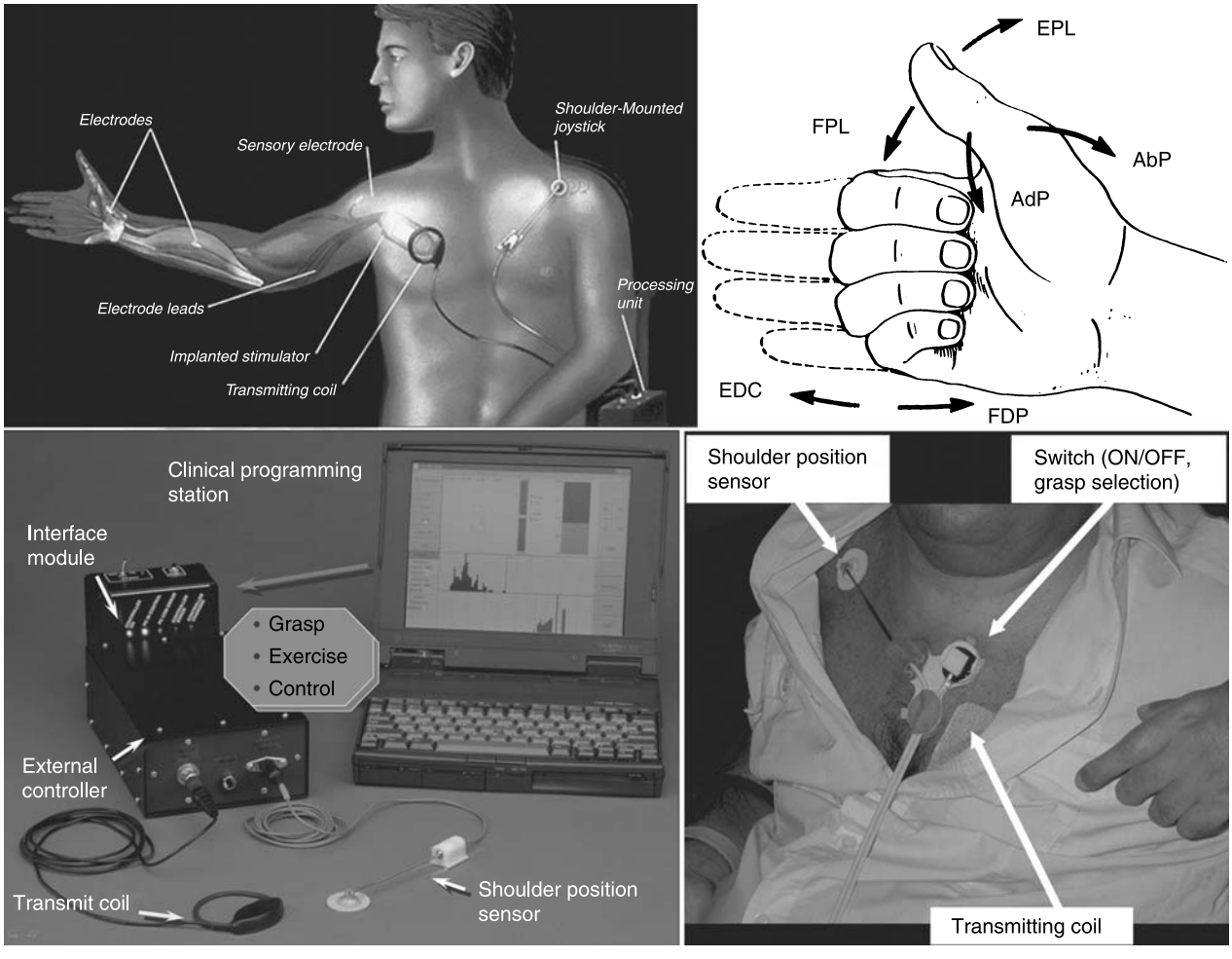

Fig. 4. The FreeHand system. *Top left*: picture of the implanted system. *Top right*: movements of the hand made possible by the system. *Bottom left*: external components. *Bottom right*: use of the transmitting coil

reconstructions of lower limb motor function associated with other spinal injury and hemiplegia [8].

The FreeHand system consists of internal and external devices (Fig. 4). Before surgery, the active and passive range of motion (ROM) is measured to investigate the applicability of a shoulder position sensor based on the ROM of the shoulder joint and the possibility of reconstruction of grasping based on the ROM of the wrist joint and fingers.

Muscle for the source of force for tendon transfer is selected by manual muscle testing (MMT). For poor extension of the forearm, posterior deltoid-triceps transfer is considered. The range of denervation is investigated. Reconstruction of hand motor function involves the muscles extensor pollicis longus (EPL), flexor pollicis longus (FPL), adductor pollicis (ADP), abductor pollicis brevis (AbPB), extensor digitorum (EDC), flexor digitorum superficialis (FDS), and flexor digitorum profundus (FDP). Peckham *et al.* call these key muscles [5, 8]. Training by TES is performed to increase the muscle strength and acquire resistance to muscle fatigue. Normally, muscles are stimulated at 25 Hz for 5 seconds followed by an interval for 5 seconds, and this cycle is repeated for 1 hour 3–5 times a day. This training is performed for 3 months. These are preoperative preparations.

Surgery is performed under general anesthesia without muscle relaxation. After avascularization of the upper arm, the extensor and flexor sides of the forearm are simultaneously incised, and the muscles and tendons are dissected and identified. The electrodes are sutured to the optimum muscle surface using an intraoperative stimulator. The receiver is implanted in the anterior thoracic region, and the lead is passed under the skin and connected. The movement is confirmed during surgery. After surgery, development of edema is carefully observed. Resting for 3 weeks after casting is necessary.

Operation of the system is initiated 3 weeks to 1 month after surgery. Conditions for individual muscles with implanted electrodes are established using a computer. The minimum stimulation level (threshold) for initiation of muscle contraction is input. When the strength of stimulation is increased, not only the target muscle but also the adjacent muscles contract, and induce movement of unexpected muscles. Since close control is impossible in such a condition, the stimulation level that induces contraction of only intended muscle is input as the maximum stimulation level. This level is the range of stimulation of the muscle. Using these stimulation levels, 2 types of grasping motion are reconstructed. While using FreeHand system in daily living, the system setting is repeated to provide easier and more comfortable control to the user. The efficacy and long-term stability of this system is very high [11].

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Neuroprostheses

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Neural prostheses in clinical practice: biomedical microsystems in neurological rehabilitation

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Summary

Technical devices have supported physicians in diagnosis, therapy, and rehabilitation since ancient times. Neural prostheses interface parts of the nervous system with technical (micro-) systems to partially restore sensory and motor functions that have been lost due to trauma or diseases. Electrodes act as transducers to record neural signals or to excite neural cells by means of electrical stimulation. The field of neural prostheses has grown over the last decades. An overview of neural prostheses illustrates the opportunities and limitations of the implants and performance in their current size and complexity. The implementation of microsystem technology with integrated microelectronics in neural implants 20 years ago opened new fields of application, but also new design paradigms and approaches with respect to the biostability of passivation and housing concepts and electrode interfaces. Microsystem specific applications in the peripheral nervous system, vision prostheses and brain-machine interfaces show the variety of applications and the challenges in biomedical microsystems for chronic nerve interfaces in new and emerging research fields that bridge neuroscientific disciplines with material science and engineering. Different scenarios are discussed where system complexity strongly depends on the rehabilitation objective and the amount of information that is necessary for the chosen neuro-technical interface.

Keywords: Neural prostheses; implant; biomedical microsystems; brain-computer-interface; motor prostheses; vision prostheses; neuromodulation; electrical stimulation; recording; nerve interface.

Introduction

Technical devices have helped physicians in diagnosis, therapy, and rehabilitation for many centuries. The use of electrical stimulation to cure diseases has been known for more than 2000 years. In ancient times, the Romans used electrical fish to alleviate pain caused by gout and rheumatism. It has been a long way to arrive at a scientific understanding of the bioelectrical phenomena in the body, the physiological mechanisms behind our senses and movements, and the pathophysiological alterations after lesions to the spinal cord or hearing and vision loss. However, it has remained a challenge to transfer this still incomplete knowledge into technical aids to restore lost sensory or motor functions, at least to a certain extent. In the late 1960s, several groups worldwide started inventing mechanisms of electrical stimulation for rehabilitation purposes. Liberson *et al.* [9] in 1961 reported the successful use of a common peroneal nerve stimulator in combination with a heel switch to relieve foot-drop after stroke. Many other groups around the world followed with strong teams in Ljubljana and Belgrade (former Yugoslavia), Vienna (Austria), London (United Kingdom) and Cleveland (Ohio, USA). In 1967, Giles S. Brindley implanted an array of 80 radio receiver stimulators beneath the scalp of a blind nurse [1] which was widely criticized [5] but opened the field for serious investigations on the feasibility of cortical vision prosthesis. Totally implantable phrenic pacemakers for ventilatory support were invented at the same time [8]. It was again G. S. Brindley [2] who reported the first stimulation of the sacral anterior roots of paralyzed persons for bladder management in 1973. Feasibility studies about stimulation of the inner ear after hearing loss from the 1960s to the 1970s led to clinical application of the cochlear implants in the 1980s.

While functional electrical stimulation in public was often associated with muscle stimulation over large surface electrodes, scientists and engineers from the very beginning worked on wireless solutions and miniaturization for implant reliability and patient benefit. Today, the

Table 1. *Summary of fully implanted neural prostheses with more than 1,000 implanted systems [13]*

Application	Number of implants	Manufacturers
Spinal cord stimulator to treat intractable pain and motor disorders	>130,000	Advanced Neuromodulation Systems, USA; Medtronic, USA
Auditory nerve stimulator to restore hearing (cochlear implant)	>55,000	Advanced Bionics, USA; AllHear, USA; Cochlear, Australia; MED-EL, Austria; MXM lab, France
Deep brain stimulator for tremor, Parkinson's disease and pain	>20,000	Medtronic, USA
Vagal nerve stimulator to treat intractable epilepsy	>17,000	Cyberonics, USA
Sacral nerve stimulator for urinary urge incontinence, urinary retention, pelvic pain and faecal incontinence	>10,000	Medtronic, USA
Sacral nerve stimulator for bladder emptying	>2500	Finetech Medical, UK
Phrenic nerve stimulator for respiration	>1600	Avery Laboratories, USA;Atrotech, Finland; MedImplant, Austria

term ''neural prostheses'' summarizes the efforts in various fields of clinical medicine and biomedical engineering for restoring of sensory and motor functions of the human body and offering new technical aids for neurological rehabilitation. Urologists, neurosurgeons, ophthalmologists and orthopedists collaborate with physicists, material scientists and biomedical engineers. Functional aspects of direct neuromuscular or sensory stimulation were complemented by therapeutical effects that led to better neurological status. Afferent nerve stimulation was added to use neuronal circuits and nerve signal processing on lower as well as on higher integration levels. This so-called neuromodulation is widely used for the suppression of urge and stress incontinence and the alleviation of chronic pain, for example.

During the last 35 years, a lot of success stories have been written, but implanted prostheses often have remained in shadow [4]. Existing clinical devices are frequently unknown to many physicians and patients, and health insurances have to be convinced to reimburse costs in each individual case. Spinal cord injury (SCI) has devastating consequences for the person involved. He or she must learn a new way of life after the hospitalization and rehabilitation phase. Activities of daily life (ADL) are more or less limited. Medical and social costs are high, but an adequate ''expensive'' neural prosthesis might help the patient to participate in daily social and economic life again and will decrease long-term costs in the end. However, unobserved by most of the media and due to the tremendous progress in microelectronics, microengineering and material sciences during the last three decades, many applications of neural prostheses have widely been transferred into clinical practice (Table 1). More than 200,000 devices have been implanted into patients [13]. Presently implant electronics are highly integrated systems. Smallest high capacity batteries work for several years and telemetric links supply high channel implants with energy and signals to control limbs and to create sound. The advancements on microsystem technology paved the way for ambitious projects like retina implant concepts with 100 stimulation channels and more fitting into a human eye. The requirements for a biostable encapsulation of these microimplants as well as innovative concepts for implant fixation or long-term functionality give room to a lot of basic and applied research on future neural prostheses. Latest efforts focus on the recording of signals from human sensors to close the loop in control tasks and to move towards a deeper understanding of how the human brain integrates the incoming information to react with the environment. Altogether, the alliance of clinical medicine and biomedical engineering in the last decades has yielded many neural prostheses that help patients to increase their ADL and participate more in social life again.

A sound standing discussion might help to carry background information into public and to promote the dissemination of neural prostheses. In consideration of an aging society, many new applications will arise in clinical practice ranging from hemiparesis after stroke to incontinence or widespread hearing and vision impairments. A broad knowledge of potentials and limitations of technical aids both from technological and ethical points of view will help relieve fear and promote the application of technical aids for an active and self-determined life.

Biomedical microsystems as interface to the nervous system

Many implants with neuro-technical interfaces have already been established in clinical practice or are still under investigation in preclinical tests (Fig. 1). Due to good experiences with materials, if the number of transmission channels is limited, most established systems

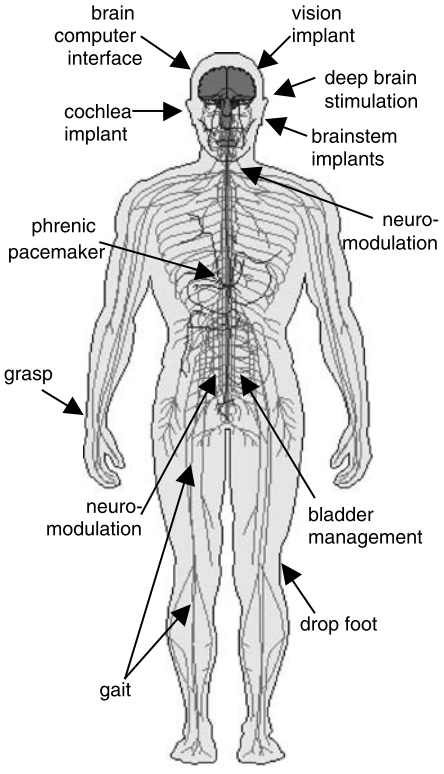

Fig. 1. Applications of neural prostheses for functional rehabilitation, neuromodulation, therapeutic electrical stimulation and as brain-machine-interface within the human body

can be fabricated by means of precision mechanics [19]. However, microsystem engineering offers opportunities for more complex systems with integration techniques for microelectronic circuits.

The major challenge for all applications is the choice of adequate materials and fabrication technologies that match the demands on chronic implants. In addition to be non-toxic in contact with the body and its fluids, materials must be biostable within the body over decades. The transduction of signals between the implant and the nerves and muscles, respectively, requires a high quality and stability level to support the patients in their daily lives and assures a constant performance of their neural prostheses. In the following comprehensive overview, the different research approaches and clinical applications [15, 16] have been structured into four groups for clarity reasons: systems for restoring motor or sensory functions, respectively, neuromodulation implants and human-computer-interfaces.

Restitution of motor functions

The restitution of motor functions such as paraplegia after spinal cord injury or hemiplegia after stroke has been subject of research since the early 1960s. It took more than 40 years to integrate the idea and the concept of ''drop foot'' therapy by electrical stimulation [9] into clinical practice using an implantable system meeting the requirements of the market [15]. The application of phrenic pacemakers that restitute breathing by electrical stimulation of the phrenic nerve was transferred into clinical practice after a short period of experimental work [8] and lets patients live and breathe without pressure ventilation or iron lung, respectively. Implants for micturition after spinal cord injury, i.e. voiding of the urinary bladder, were invented in the 1970s, and implant numbers increased quite fast [3]. So far, even though many microelectronic components have been integrated into neural prostheses, the neuro-technical interfaces themselves are still fabricated by means of precision mechanics and have proved their stability in clinical practice over decades [15]. Micromachined neuro-technical interfaces, however, are subject of intense research [6, 12, 14, 16]. The ''BIONs'' (Bionic Neurons) are the first implantable microsystems. These single channel stimulators are implanted in target muscles with a biopsy needle. Data transmission of stimulation parameters and energy supply is realized via an inductive link. Theoretically, up to 256 BIONs might be controlled with a single extracorporal transmission coil. They are currently under clinical test to treat incontinence and to prevent shoulder subluxation after stroke. Latest developments of these technically highly sophisticated implants with a diameter of 2 mm and a length of 16 mm contain a rechargeable battery.

The Freehand System® (Neurocontrol Corporation, Cleveland, OH, USA) restored grasp after spinal cord injury between the 5th and the 6th cervical vertebrae (C5/C6) by means of functional electrical stimulation. Implanted epimysial electrodes on the muscles of the hand and forearm restituted cylinder and pinch grip of the hand [15, 19]. About 270 of these neural prostheses had been implanted successfully in the USA and Europe before the product was withdrawn from the market for economical reasons.

Research activities worldwide are focussing on the replacement of muscle electrodes by sophisticated nerve electrodes to reduce energy demand and increase the degree of selectivity to obtain more numerous and finer grasp patterns. With the introduction of microsystem technologies, multi-channel electrodes with integrated control electronics (Fig. 2) were developed on flexible, polymer based printed circuit boards and electrode substrates. Polyimide proved to be a good substrate material

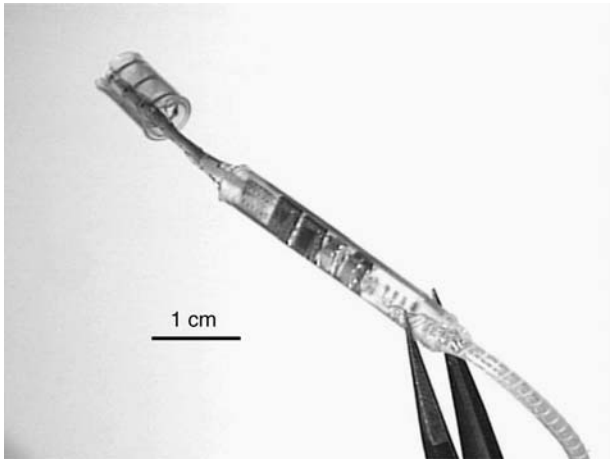

Fig. 2. Multipolar cuff electrode with a hybrid integration of control electronics assembled on a polyimide substrate and silicone rubber encapsulation [17]

with respect to surface and structural biocompatibility [18]. Additionally, it showed a good biostability in chronic implantations [12].

Not only has access to nerves by neural prostheses for control purposes been subject of research for more than 30 years but also the establishment of stable interfaces to nerves after amputation trauma in order to control artificial limbs. Microtechnical approaches of silicon- and polyimide-based [17] sieve electrodes accomplished contact between regenerating nerves and technical microsystems [12] in experimental animal studies. They are highly sophisticated neuro-technical interfaces but not the only ones to record signals of the remaining nerves after amputation trauma. Intrafascicular nerve electrodes (LIFE) which are placed longitudinally between the fiber bundles offer an excellent alternative [12, 15, 16]. In first clinical tests, amputees controlled a virtual analog of an artificial hand prosthesis with nerve signals recorded from their nerves.

Restitution of sensory functions

Both engineers and physicians have been working for decades on the restitution of lost sensory functions of the body after trauma or disease. More than 60,000 patients have been implanted with cochlear implants to restore hearing after loss of the outer hair cells [23].

Restoration of sight after diseases that led to blindness is a particular challenge. More than one million sensor cells – the rods and cones – transduce the incoming light in the retina into graded potentials. The overlying cell layers perform preprocessing and pulse coding before the signals are finally fed into the optic nerve and travel towards the visual cortex passing the lateral geniculate nuclei (LGN) as relay stations. The implantation site of a neural prosthesis has to be chosen depending on the trauma or disease that was the cause of blindness. The fundamental work that proved the feasibility of such implants was done in 1929. In human experiments *Foerster* showed that localized visual cortex stimulation leads to the perception of pea-shaped light sources, the so-called phosphenes. Currently, research concentrates on developments in neural prostheses for patients suffering mainly from retinitis pigmentosa, a hereditary disease where the sensor cells of the retina degenerate. The visual field decreases gradually from the periphery and finally leads to complete blindness. So far, there is no therapy for about 1.5 million patients suffering from this disease. Primarily, three different implantation sites have been established over the last ten years of research [20]: the retina, the optic nerve and the visual cortex. The first experimental work to interface the human visual cortex was done more than 30 years ago. In key experiments, *Brindley* showed the feasibility of a cortical vision prosthesis with wireless energy supply and signal transmission in a blind human volunteer [1].

Microsystem technologies have been used to develop electrodes for focal cortical stimulation with high spatial selectivity. These latest technologies offer many advantages over precision mechanics. Microelectronic circuits have been monolithically integrated into silicon-based electrodes. The small electrodes need less energy for a focal stimulation and the foci are much smaller. An increase in electrode numbers and a decrease in electrode site areas are technologically easy to perform.

Optic nerve prostheses as well as retinal vision prostheses require the presence of the inner retina with intact ganglion cells that form the axons of the optic nerve. The surgical intervention for interfacing the optic nerve is quite sophisticated. Veraart *et al.* showed the feasibility of optic nerve prosthesis with a cuff electrode. Even though the nerve with a diameter of 2 mm is composed of more than 1 million fibers, superficial electrical stimulation with a four site cuff electrode was sufficient to induce visual sensations that correlate with the stimulation site and exhibit a certain spatial resolution [20]. A blind retinitis pigmentosa subject was implanted and trained for several months. She is now able to differentiate defined objects of daily life in a test environment. However, due to the sophisticated implantation procedure and the low resolution, this approach can only be recommended for individual cases. Especially here, groundbreaking technological innovations are highly

appreciated before implants could be transferred into clinical practice. Worldwide, many research groups and companies are working on the development and commercialization of retinal vision prostheses [16]. Microsystems engineering has developed technologies which allow miniaturization of implants to a degree that electrodes could be placed under the retina (subretinal) or directly onto the retina (epiretinal). In the subretinal approach, stimulation devices were implanted under the retina to excite the remaining neuronal structures by means of electrical stimulation and thereby replacing the physiologic function of the degenerated sensor cells. This stimulation of the visual system on a low level allows the use of the (biological) signal processing of the higher levels within the retina and the proceeding relay stations up to the visual cortex. These vision prostheses consist of a microphotodiode array with integrated stimulation electrodes. The incoming light is measured and light intensity is transferred into adequate stimulation pulses to excite the adjacent nerve cells [24]. Originally, it was assumed that the ambient light would be sufficient to stimulate the retina via the implanted photodiodes. In the meantime, it has been proven that the light density from ambient light is not sufficient to exceed the stimulation thresholds and to excite the nerve cells. The German group around *E. Zrenner* (Tuebingen, Germany) chose an approach with an additional infrared diode for energy supply. Ambient light only selects the electrode and determines the corresponding stimulus amplitude [16]. The implantation procedure penetrates the sclera from the back of the eye globe (ab externo) or is done from the inside of the eye globe after vitrectomy (ab interno). Both interventions ensure stable placement of the vision prostheses after implantation. Reproducible signals with a spatial resolution were recorded from the visual cortex in cats and pigs after electrical stimulation of the retina by the implant.

Groups in Australia, the USA and Germany are working on the development of an epiretinal vision prosthesis. Since 1995, a German consortium has developed a microsystem with an inductive link for energy supply and data transmission for implantation in the eye. Spectacles with an integrated camera form the extracorporal counterpart of the implant for energy and data transmission. The first version of the vision prosthesis is based on a flexible polyimide substrate with integrated electrodes and a hybrid assembly of the electronic circuits (Fig. 3). The receiver for data and energy is placed into an artificial intraocular lens. Thin and flexible leads interconnect to the stimulator chip and the stimulation

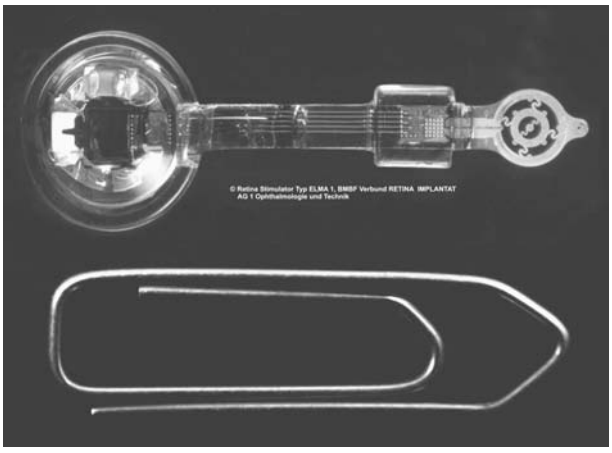

Fig. 3. Epiretinal vision prosthesis; a hybrid assembly on a polyimide substrate (EPI-RET consortium, Germany) [18]

electrodes which are placed directly onto the ganglion cell layer [18]. The implantation procedure and the surgical intervention are highly sophisticated, but they are feasible for ophthalmologists with adequate manual skills and stable implants were placed long-term on the retina. Current vision prostheses consist of 25 electrode sites. A spatially selective excitation of the visual cortex after retinal stimulation with a wireless implant has been done [21]. The second generation of the implant with a higher integration density is under development [11].

Six completely blind retinitis pigmentosa patients have been implanted with a 25-channel implant from Second Sight, Inc. (Valencia, CA, USA). After a training phase, the subjects were able to recognize the orientation of patterns and recognize different objects of daily life within a predefined test environment.

Neuromodulation

The greatest success stories on neural prostheses are nearly unknown to the public [4]. Such neural implants work in more than 100,000 patients to improve quality of life and increase activities of daily living by so-called neuromodulation, the electrical stimulation of ascending (afferent) pathways or central nervous structures to modulate nerve activity [13, 15]. This method is based on the gate control theory for pain as it was proposed by Melzack and Wall in 1965. It states that a mechanism in the dorsal horns of the spinal cord acts like a gate which inhibits or facilitates transmission from the body to the brain on the basis of the diameters of the active peripheral fibers as well as the dynamic action of brain processes. The gate control theory, however, is not able to explain several chronic pain problems, such as phantom

limb pain, which require a greater understanding of brain mechanisms. Therefore, more sophisticated theories are under investigation. However, since its introduction in 1967, the stimulation of the spinal cord has become the most successful application in the field of neural prostheses. Methodology and technology of spinal cord stimulation for the management of chronic, intractable pain have evolved continuously. To overcome dissatisfactory pain paraesthesia with single electrode implants, new approaches were developed in the late 1990s attempting to selectively cover one or more dermotomes with paraesthesia as well as to provide sequential stimulation of different anatomic sites. These approaches have been applied both intraspinally and extraspinally by stimulating either the spinal nerves or the dorsal columns. Today, more than 130,000 implants help patients to treat intractable chronic pain [13]. A second group of patients that benefit from spinal cord or sacral root stimulation suffer from urinary incontinence. More than 10,000 patients have already been treated. The implant technology has been derived directly from the state of the art pacemakers and is produced by Medtronic (USA) and Advanced Neuromodulation Systems (USA), which are the main manufacturers.

Deep brain stimulation has become a clinical method for the management of some of the clinical problems of Parkinson's disease. After bilateral stereotactic implantation of guide wire with electrode sites in brain regions of the basal ganglia and thalamic or subthalamic nuclei, chronic tremor is suppressed and dyskinesia is overcome in many patients. The application of deep brain stimulation is a good example for modification of already existing components to introduce an implant system for completely new applications. Implants were derived from cardiac pacemaker technology. They consist of titanium housing with stimulator electronics and a battery power supply to be implanted in the chest area. The electrodes are connected with the implant via subcutaneous cables with plugs, one in the brain region and another near the implant. The system can be programmed via a telemetric link and can be switched on and off by the patient via a magnet that is moved over the body region of the implant. So far more than 20,000 patients have been implanted.

After years of clinical experience, (psychiatric) side effects of this therapy have become apparent including depression, mania, aggressions and deficits in language. For their own safety, some patient groups should be excluded from the therapy. The implantation of a DBS does not seem to interfere with pre-implanted cardiac pacemakers if the receivers for telemetric programming are placed at a distance greater than 15 cm from each other. In order to assess the long-term performance and to balance benefits and side-effects, the stimulus parameters have to be carefully adjusted in the postoperative period.

Fig. 4. Implant for vagal nerve stimulation (Cyberonics, Inc., Houston, Texas, USA)

Vagus nerve stimulation (VNS) was introduced into clinical practice in 1997 with the neurocybernetic prosthesis system (NCP) from Cybernetics, Inc. (Houston, Texas, USA). It is an implantable, multi-programmable pulse generator that delivers constant electrical signals (Fig. 4). The signals are delivered on a predetermined schedule, or may be initiated by the patient with an external magnet. The device is implanted in a subcutaneous pocket in the chest just below the clavicle, similarly to pacemaker placement. The stimulation signal is transmitted from the prosthesis to the (left) cervical vagal nerve through a lead connected to an electrode which is a multi-turn silicone helix with a platinum band on the inner turn of one helix. Also this system was grown out of pacemaker technology and does not represent a technological breakthrough.

Stimulation of the vagal nerve is used for the treatment of many diseases as this nerve has many diffuse projections to mid-brain and cortical regions. So far, more than 17,000 NCPs VNS have been implanted to treat intractable epilepsy in adults as well as in children. Other proposed applications include depression, pain, eating disorders like obesity, migraine, dementia, and Parkinson's disease. Many results are promising but side effects have also developed. These include day sleepiness due to apneas and arousals associated with the stimulation. Heart rate variability may occur after long term

stimulation and pain thresholds can be decreased; the first side effect is now under investigation to control the heart beat frequency in some diseases. However, advantages mainly prevail as increasing numbers of implanted patients have shown.

Humanecomputerinterfaces

The implantation of penetrating microelectrodes in the human cortex, the so-called human-computer-interfaces, offers a new category of interfaces to the brain compared to the non-invasive methods derived from EEG techniques. For more than two decades, miniaturized electrode arrays have been implanted in acute and chronic animal experiments in different parts of the brain like hippocampus, cerebellum and cortex. So far, only one electrode array has been implanted per experiment. Connection to the signal processing electronics was cable bound. Up to now only acute human implantations for pilot studies appeared to be feasible. However, in the fall of 2004, a 100-channel electrode array, originally developed at the University of Utah (Salt Lake City, UT, USA) several years ago [10], was commercialized by Cyberkinetics, Inc. (Foxborough, NJ, USA). This has been implanted in human subjects suffering from high spinal cord lesion (C3). These patients are now able to communicate via these interfaces, but communication speed is still fairly slow, about 20 letters per minute. Developments at the Illinois Institute of Technology (Chicago, IL, USA), in cooperation with the Huntington Medical Research Institute (Pasadena, CA, USA) show the feasibility of implants with up to 1024 wire electrodes that are grouped to ensembles of 8 and connected with wires to implantable microelectronic circuits. The University of Michigan (Ann Arbor, MI, USA) chose microsystem technologies to develop shaft- and comb-like electrode substrates with multiple electrode sites per shank and to fabricate three-dimensional hybrid assemblies (Fig. 5).

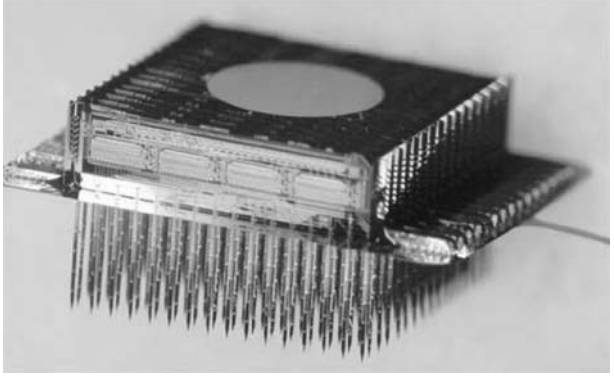

Fig. 5. Three dimensional neural prostheses to interface the brain; silicon substrate with integrated microelectronics for 1024 electrode sites and 128 data channels [20]

Microelectronic circuits have been integrated into these complex microsystems to amplify, filter, and multiply the signals near the electrodes. Additionally, a signal-processing chip for detection of action potentials has been developed to further reduce the amount of data and allow telemetric data transmission via inductive link [20]. These arrays can also be used as distributed implants. Application scenarios for these implants include brain-machine-interfaces in the (pre-) motor cortex for control purposes ranging from simple switches within communication tasks up to on-line control of artificial limbs. Visionary scenarios also explore the communication between distant brain areas. While present brain-machine-interfaces record neuronal signals only, future devices might also be developed as bi-directional interfaces. Recording and electrical stimulation will be implemented allowing the stimulation of the somatosensory cortex to give feedback information of the grasping force and the position of an artificial limb to the patient.

Conclusions

Research on biomedical microsystems for neural prostheses and human-computer-interfaces is a highly innovative area. New materials and latest knowledge from neurosciences has been combined in experimental and preclinical studies. Retinal implants and simple human-computer-interfaces, however, are currently undergoing commercialization. Transfer of biomedical microsystems into neural applications for clinical practice should be expected in the near future. Only future patients can tell about the performance and the real benefits of those neural prostheses during activities of daily living.

For those who would like to get a more detailed insight into the theory and practice of neural prostheses, latest publications in textbooks from Horch *et al.* [7] and Stieglitz and Meyer [15, 16] are recommended for further reading.

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Neuroprosthetics of the upper extremity – clinical application in spinal cord injury and challenges for the future

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Summary

The complete restoration of movements lost due to a spinal cord injury (SCI) is the greatest hope of physicians, therapists and certainly of the patients themselves. Particularly, in patients with lesions of the cervical spinal cord every little improvement of missing or weak grasp function will result in a large gain in quality of life. Despite the fact that novel drugs for axonal regeneration in the spinal cord are in the phase of imminent human application, up to now, the only possibility of restoration of basic movements in SCI persons consists in the use of functional electrical stimulation (FES). While FES systems in the lower extremities for standing or walking have not reached widespread clinical acceptance yet, devices are available for demonstrable improvement of the grasp function. This applies to tetraplegic patients with stable, active shoulder function, but missing control of hand and fingers. Particularly, with the use of implantable systems a long-term stable, user-friendly application is possible. Most recent work aims at the development of minimally invasive, subminiature systems for individual functional support. The possibility of direct brain control of FES systems will extend the application of grasp neuroprostheses to patients with injuries of the highest cervical spinal cord.

Keywords: Spinal cord injury; tetraplegia; functional electrical stimulation (FES); neuromuscular electrical stimulation (NMES); neuroprosthesis; implantable electrode; surface electrode; grasp restoration; user interface; brain-computer interface.

Introduction

The incidence of traumatic and non-traumatic spinal cord injuries in industrial countries is around 40 new cases every year per million population [13]. In Germany, there is an estimated number of 60,000 people who have a spinal cord injury (SCI) with 1,800 new injuries each year [2]. Of these patients, 40% are tetraplegic with paralyses affecting not only the lower extremities (thereby causing restrictions in standing and walking) but also the upper extremities and hence resulting in limitations of grasp function. The total loss of grasp function associated with a complete or nearly complete lesion of the cervical spinal cord leads to an all-day, life-long dependency on outside help and thus represents a tremendous reduction in the patients' quality of life. Any improvement of lost or limited functions is highly desirable not only from the patients point of view [1] but also for economical reasons: the average costs during the first year in a case of high tetraplegia (C1–C4) reach up to 710,000 US$ and up to about 458,000 US$ in a case of low tetraplegia (C5–C8) [13]. These figures together with the fact that tetraplegic patients are often young persons [4] underline the significance of restoration of these functions, and the grasp in particular, as one of the primary goals of modern rehabilitation medicine.

Recent advances in the basic sciences currently open new doors to the clinical introduction of novel drug therapies for spinal axonal regeneration and raise hope for a partial repair of spinal cord injuries in the near future [19, 24]. However, the safety of these approaches remain to be proven in clinical trials and the extent of neurological recovery in humans still is not clear. Thus, up to now functional electrical stimulation (FES) is the only clinically applicable method for at least partial restoration of the grasp function. In recent years, several FES systems of various levels of complexity have been introduced in the clinical environment. These FES systems deliver short current impulses eliciting action potentials on the efferent nerves; the latter provoke contractions of the innervated, yet paralyzed muscles of the hand and the forearm. On this basis, FES artificially compensates for the loss of voluntary muscle control.

FES systems with surface electrodes

The easiest way of improving a weak or lost grasp function is the application of a multi-channel, transcutaneous electrical stimulation. For this form of stimulation several technical systems – so called neuroprostheses – have been developed over the last decade. The first commercially available systems include the H200 (formerly called Handmaster, NESS Ltd., Ridderkerk, Netherlands, Europe), the ActiGrip®-system (Neurodan, Aalborg, Denmark, Europe), and the Bionic Glove [16, 18, 21]. Generally, the major advantage of these non invasive systems is that they can be offered to patients for temporary application at a very early stage of primary rehabilitation. However, the functional outcome of systems based on surface electrodes is limited: they have the disadvantage of insufficient selectivity in terms of stimulating individual muscles, difficulties with daily reproduction of movements, limited excitability of deeper muscle groups and pain sensations. Additionally, patients describe the handling of the electrodes as being complicated. Therefore, these systems have not gained long-term acceptance in everyday life conditions [17]. Most of these restrictions are relieved by the use of percutaneous, intramuscular electrodes. However, long term experiments with this kind of electrodes revealed major problems due to the increased risk of inflammation at the point of insertion and, in cases of chronic use, high risk of mechanical failure of the thin wires [6, 11]. All of these restrictions with surface and percutaneous electrodes led to the development of implantable neuroprostheses for restoration of motor functions, where electrodes, cables and the electrical stimulator are surgically placed under the skin. With an overall number of 312 implantations so far the Freehand® system (Neurocontrol Corp., Valley View, OH, USA) is the most widespread representative of an implantable neuroprosthesis for restoration of the grasp function. The Freehand® system was introduced in Cleveland/USA by the research team of Peckham, Mortimer and Keith [7, 20] and was commercially available in the US after its FDA approval in 1997 and in Europe after its CE-certification two years later. While the first systems have now been operating for over 12 years, the commercialization of the system stopped in 2001 not for clinical, but for financial reasons.

Implantable FES systems

In February 1999, at the Orthopaedic University Hospital II in Heidelberg, we implanted a Freehand® system for the first time in the German-speaking countries; a total number of 7 implantations has followed in Germany so far. The Freehand® system consists of implantable (Fig. 1) and external components (Fig. 2): The parts permanently residing under the skin of the patient are the epimysial electrodes made of platin-iridium together with integrated cables and the electrical stimulator. The electrode cables are silicon isolated spiral cables manufactured in a dual helix structure, which guarantees high extensibility and tensile strength and consequently minimises the risk of cable failures [8].

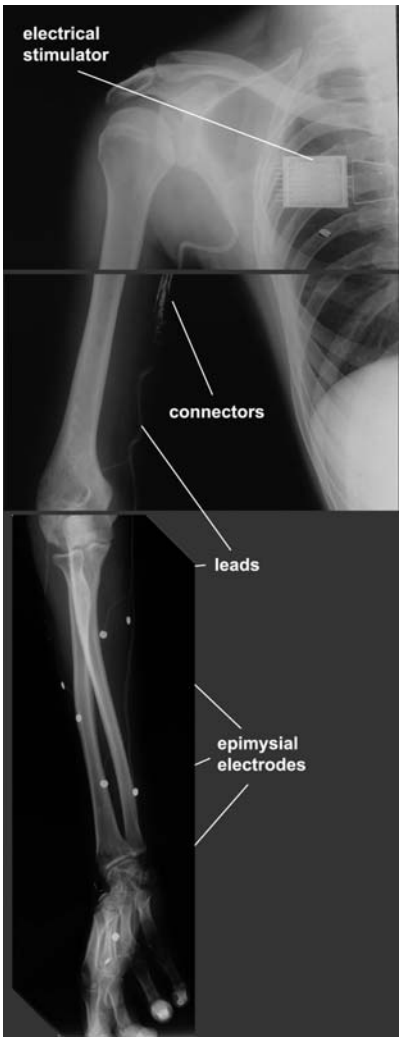

Fig. 1. X-ray of stimulator, cables and electrodes of the Freehand® system

The first version of the implantable stimulator provides eight independently controllable stimulation channels and the titanium case serves as common anode. The second, not commercially available version has 12 channels. Each channel delivers rectangular, constant-current pulses with an exponential charge balancing pulse (frequency either 12 or 16 Hz). In contrast to the first version, which is an exclusive receiver system, the second

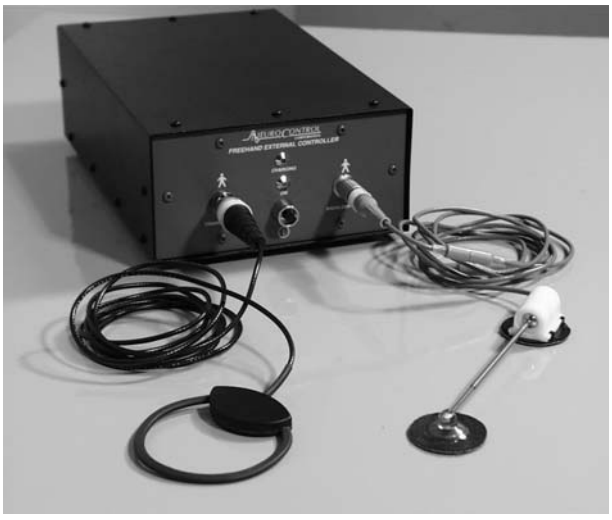

Fig. 2. Overview of the external components of the Freehand® system

version of the implant provides the possibility for bidirectional data flow. Thus, control parameters and analog data from two acquisition channels can be transmitted from the implant to the external transceiver. The stimulator contains neither an internal power source nor a programmable electronic device like a microcontroller. This design was chosen to avoid the need to exchange the implanted stimulator in case of an empty battery or a lack of processing power. However, the inherent option for an easy upgrade without removing any implanted parts allows the system only to be operated in combination with external control components [20]; the external components consist of an external control unit (ECU), an induction coil and a shoulder position sensor (Fig. 2).

The external control unit is based on a microcontroller with an integrated power source, which delivers power and control commands to the implanted stimulator. Transmission of energy and of control signals is performed by the induction coil, which is placed directly onto the skin over the region of the stimulator antenna. The shoulder position sensor (two axis hall-sensor) is fixed externally on the contralateral shoulder and records forward/backward and upward/downward movements of the shoulder.

Patients' prerequisites

For a better understanding of the possibilities and the limitations of the Freehand® concept, the status of a 40-year old patient with a traumatic (car accident 1998), complete tetraplegia (ASIA A) below C5 is presented in detail. He was classified an ''ideal'' candidate for implantation for the following reasons: He has a stable shoulder function (M. deltoid ant. 4/5; M. deltoid middle 5/5; M. deltoid post. 4/5), no severe limitations in the range of motion in his shoulder, elbow, hand or finger joints and negligible spasticity. It is a general requirement that the patient needs to be skeletally mature and neurologically stable. Because of the latter, we believe that the decision on implantation of any FES system should not be made before two years after injury. Our patient was able to actively flex the elbow (M. biceps 5/5; M. triceps 0/5; M. sup. 3/5; M. pron. ter. 1/5) of his right and left arm but had no voluntary hand or finger function (M. ext. carpi rad. 1/5; M. ext. carpi uln. 0/5; all wrist flexors 0/5; all finger extensors and flexors 0/5; extrinsics 0/5; intrinsics 0/5). This neurological status is typical for patients with a C5/6 lesion, who have a stable shoulder and sufficiently active movements for placement of the hand in space but no function of the hand and fingers (International Classification Group 0). The neurological status of his right and left hand were comparable. We decided to restore the grasp of his right hand, because this was his dominant hand prior to injury. Due to the longsome, extensive pre- and postoperative training in combination with a stay in hospital for up to 3 months only patients with a high degree of motivation and a firm private background may want to take part in the program. After examination of the orthopedic prerequisites (range of motion, muscle strength, joint contractures), a check of the electrical excitability of the relevant muscle groups is mandatory. With an accurate current/pulswidth-diagnostics the status of innervation of the paralyzed muscles is tested by using short current pulses. The results of this testing are of utmost importance, because only muscles with an intact secondary motor neuron (exclusion of plexus paresis) are usable by currently available FES systems.

Preoperative muscle conditioning

Since the patient's key muscles for grasp restoration responded adequately to short current pulses with no signs of denervation except for M. ext. carpi rad., the preoperative training program was initiated. By use of a 3 channel surface electrical stimulation of the three main nerves of the forearm i.e. nerve radialis, medianus, and ulnaris, the flexor and extensor muscles of the hand, the thumb and the fingers are stimulated in an alternating manner. The primary goal of this stimulation regime is the training of the paralyzed muscles while avoiding any excessive fatigue during each training session. Whereas at the beginning of the stimulation program the mus-

a b

Fig. 3. (a) Lateral grasp for handling of small objects like a fork, pen etc. (b) Palmar grasp for handling of larger objects like a cup, video cassette etc

cles of the patients are typically fatigued after one daily training session of only 10 min with a pulse frequency of 2–6 Hz (single twitches), the stimulation parameters can be continuously increased over a period of 16 weeks. Shortly before the surgery, two daily sessions, 2 hrs each with a stimulation frequency of 20 Hz (tetanic contractions) should be accomplished without any signs of fatigue of the muscles. The achieved fatigue resistance builds the basis for the postoperative functional performance of the Freehand® system. The preoperative training program is performed at the patients' home with support of a helping person and regular examinations in the hospital for the adjustment of the stimulation parameters.

Implantation of the Freehand® components

The implantable components are inserted during an operation of up to 10 hrs. After determination of the optimal placement of the electrodes through an intraoperative muscle mapping, the 8 epimysial electrodes are fixed on the appropriate muscles. In this patient, the electrodes were placed on the M. abd. poll. brev., M. add. poll., M. flex. poll. long., M. abd. poll. long. to realise movements of the thumb in all directions and on the M. ext. dig. comm. for extension, the M. flex. dig. prof. and M. flex. dig. sup. for flexion of the fingers. With this electrode configuration the restoration of two different grasp patterns is possible. First, a lateral grasp, where small or flat objects are hold between the flexed fingers and the flexing thumb and second, a palmar grasp, where larger objects can be picked up between the flexing fingers and the adducting thumb (Fig. 3a and b).

The 8th electrode was placed on the M. ext. carp. uln., which was transferred to the distal tendon of the M. ext. carp. rad. and thereby transformed into a wrist extensor. This configuration was chosen because the patient had very weak wrist extensors (almost completely denervated M. ext. carp. rad. 1/5) and therefore another muscle should be used for stabilization of the wrist during contraction of the strong finger flexors. If the 8th electrode is not necessary for wrist stabilization it can also be configured as a so called sensory electrode. This electrode is then placed in the shoulder region, where the patient has unlimited sensation with the metal electrode surface in direction to the skin. The stimulation frequency of this electrode is set according to the actual command signal and therefore provides a kind of sensory feedback of stimulation strength. In the last few years, with the number of implantations increasing, surgeons make only minor use of this option because patients are able to control their grasp movements much more easily and quickly by visual feedback. The operation terminates with the connection of the electrode cables and the electrical stimulator, which is fixed under the skin in the insensible area of the chest.

Tenodeses and muscle transfers

One main component of the Freehand® concept is the integration of tenodeses and muscle transfers. Since the Freehand® system is only capable of restoring the actual grasp function of the hand, the active, voluntary extension of the elbow, which is normally missing in patients with lesions higher than C6, has to be achieved by tendon transfers (M. deltoideus posterior to M. triceps). Generally, an insufficient active wrist extension may also be enhanced by appropriate tendon transfers. In our case we did a transfer of the M. brachiorad. to M. ext. carpi rad. (3/5) for achieving an active wrist extension.

Also, the IP-joint of the thumb was stabilized by performing a split-FPL(M. flex. poll. long.)-tenodesis. All necessary tendon transfers are done as an all-in-one procedure during the surgical implantation of the Freehand® components.

Postoperative functional training

After immobilization of the arm to allow time for tendon transfer healing and stabilization and encapsulation of the electrodes and the stimulator, training of the muscles with the implanted components was started 4 weeks post surgery. After another 4 weeks, functional training with an adjustment of the stimulation and control parameters to the individual conditions of the patient was possible. At the end of a 10-weeks postoperative rehabilitation program, the patient had gained a substantial functional benefit [14, 22]. The patient is now able to perform activities of daily living like eating or writing completely on his own without any dedicated aids or devices. He is not depending on the help of carers all the time, which results in a big improvement in his quality of life.

User interfaces of neuroprostheses

One of the main criteria for acceptance of technical aids in everyday life is a reliable, autonomous control by the handicapped person her/himself. This also applies to neuroprostheses, where individually adaptable user interfaces with different technical complexity are existing.

Control by artificial movements

The easiest way of controlling a neuroprosthesis is by switching through the phases of a dedicated stimulation sequence by pressing a manual switch fixed at an appropriate position on the wheelchair or walker [10]. However, with this kind of interface it is not possible to achieve a graduated control e.g. of the grasp pattern and the grasp force. The developer of the Freehand® system therefore have incorporated another way of control: The hand opening/closing is controlled by the patient through forward/backward movements of the contralateral shoulder, which determine the degree of hand opening/closing by proportional control. If the patient wants to lock the current position of the hand for grasping an item with constant force, she/he lifts her/his shoulder with a quick upward movement. If the system is locked in this way, the patient is able to move her/his shoulder with reasonable velocity without the risk of loosing grasped items. The unlocking occurs in the same way as the blocking through a quick shoulder jerk. An additional switch is integrated into the shoulder joystick, which permits the patients to switch between two grasp patterns (lateral and palmar grasp, Fig. 3a and b) through a short press and the activation/inactivation of the whole system through a long press.

Control by residual electromyogram (EMG)

Most of the clinically established control methods are based on the use of auxiliary movements that are not directly related to the target movement. The more complex these auxiliary movements are – like the shoulder movements for control of the Freehand® neuroprosthesis – the more concentration is necessary from the user. This makes training times longer and regular use of the system less comfortable. Therefore, it would be desirable to have a more ''natural'' control of movements. A step in this direction has been taken for the Freehand® system, where the degree of wrist extension could be used for a ''natural'' proportional control instead of the artificial control via the shoulder movements [5]. However, this option is only available in patients with a strong active wrist extension who – if treated adequately in the first month after injury – normally develop a passive tenodesis grip. A passive tenodesis grip evolves from active extension of the wrist and passive closing of the fingers and thumb. Patients with a strong passive tenodesis grip are very skilful after intensive occupational therapy. In these cases, the additional functional benefit through the use of an implantable neuroprosthesis should be carefully analysed and considered in relation to the necessary efforts concerning time and money. During several screening sessions with potential Freehand® users, we have seen many patients exhibiting weak voluntary contractions of forearm muscles; these contractions were palpable but without any functional relevance. The opportunity of using this residual muscle activity as a command signal is most appreciated by the user because the muscles are directly involved in the aimed movement. For this purpose, high sophisticated technical solutions have been developed in the last few years. These solutions are based on recording the low-amplitude EMG of a partially paralysed muscle, amplifying it and applying the processed signal for control of either amplitude or pulse width of the FES device [23]. With this method, a force amplification system can be build up; an example is the restoration of a passive tenodesis grip by recording

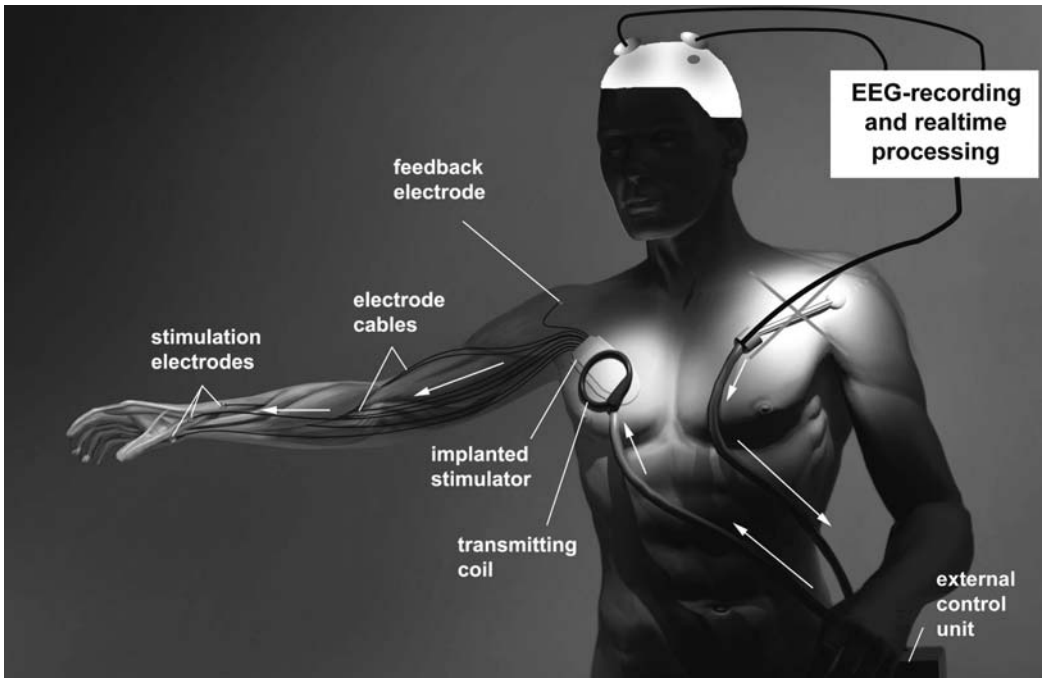

Fig. 4. Replacement of shoulder joystick with a brain-computer interface for "thought"-control

the residual voluntary EMG of the M. ext. carpi rad., blanking stimulation artifacts, calculating the muscle activity and thereby controlling the stimulation of the same muscle to achieve a dorsal extension of the wrist and the associated tenodesis grip.

Direct brain control

In case of high cervical spinal cord injuries above C4, only very few active muscle functions, that can be used for the control of a neuroprosthesis, are preserved. Conversely, in these high lesioned patients, more numerous degrees of freedom must be controlled because, in addition to the hand and fingers, the elbow and shoulder function must also be restored by FES. A novel approach for solving this contradiction is the coupling of the neuroprosthesis with a Brain-Computer Interface (BCI). A BCI system transforms cortical activity over specified areas of the brain into control signals in real-time. An example of a realisation of a non-invasive BCI system based on EEG-recordings over the primary motor cortex is the Graz-BCI [25]. This system makes use of the characteristic oscillatory activity which is generated over specified motor cortex areas not only during execution of a dedicated motor task but also during imagery of the same task. This means that oscillations e.g. over the foot area of the motor cortex (Cz) can be voluntarily activated by imagination of foot movements and therefore can be used as a control signal ("brain-switch") for a neuroprosthesis. The feasibility of the proposed combination of a BCI system with either a neuroprosthesis using surface electrodes or the implantable Freehand® system (Fig. 4) for restoration of grasp function in tetraplegic patients has been demonstrated recently [12, 15].

Currently, the skill of controlling an EEG-based BCI system has to be learned through many extensive training sessions. Furthermore, the speed performance of these systems is low comparable to previously described methods. Taking into account the performance of current BCI systems, we conclude that whenever voluntary movements have been preserved, these movements should be used for control purposes instead of the brain oscillations. Nevertheless, in high-lesioned patients, BCIs may be the only alternative.

Conclusions

The successful application of neuroprostheses requires that several prerequisites should be fulfilled: First, an accurate muscle conditioning program should be set up to get a precise picture of the expected functional outcome. It is of utmost importance to match the possibilities of the currently available systems – in particular of implantable systems – with the expectations of patients. In patients with extended residual functions, e.g. a passive tenodesis grip in patients with a strong active wrist extension, a critical cost-benefit balancing is necessary to avoid disappointments. In our experience, successful work with the patients is not possible without the cooperation of an interdisciplinary

team consisting of physicians, therapists and technicians. Hence, we believe that implantation of neuroprostheses should be restricted to a few spinal cord centers, which possess the necessary infrastructure in order to operate as ''centers of excellence''. However, successful application of neuroprostheses does not only depend on the clinical setting. It is very important to cooperate with a reliable, professional industry partner, who does not only organize sales but also ensures long-term availability of replacement parts and also works for the rapid transfer of novel research results into commercially available products. The continuous supply of replacement parts over many years is of great importance to the patients relying on this support and to the entire community.

Despite all these restrictions, neuroprostheses for improvement of grasp function in tetraplegic patients who have preserved shoulder function but have lost hand and finger function, are available in the clinical environment. With these systems, the patients regain a high degree of autonomy in everyday life. This is especially true for implantable systems which have proven their usefulness and suitability for chronic daily use. Although restoration of the grasp function by use of neuroprostheses is nowadays possible, the utilization of the same technology in the lower extremities for standing and walking causes great problems. The unstable body posture is primary cause of a continuous risk of falls. The simultaneous activation and non-physiological recruitment of all fibers of a muscle due to the artificial excitation through external electrical impulses, the restriction of blood flow and the high forces needed for body weight bearing lead to premature muscle fatigue. This is why at the current state, even after extensive training, patients are only able to walk a dozen steps with the use of a neuroprosthesis. From the clinical point of view, this does not represent a realistic alternative to the wheelchair.

Challenges for the future

When defining future strategies for the development of novel neuroprostheses, researchers should take into account that, in most SCI patients, an incomplete lesion of the spinal cord occurs [13]. Twenty-five years ago, almost 70% of the SCI population in Germany had complete loss of motor and sensory functions below the level of lesion; nowadays, however, this percentage has decreased to less than 30% [2]. This means that the majority of the patients preserve a degree of motor control, which can be used for functional activities. In these patients, minimal invasive systems are needed, which can be adapted to their individual needs. These systems should be built as modular, one channel, network-compatible devices, to support patient-specific functional limitations rather than to substitute complete motor functions. The first promising developments towards this direction have been released recently [9] and some of them will be commercially available in the near future e.g. ActiGait® (Neurodan, Aalborg, Denmark). However, these concepts must prove their usefulness and efficacy in clinical trials. Regardless of their specific differences, all these systems should be controlled in a ''natural'' way by using the residual voluntary functions in such a way that training times could be reduced and handling become more comfortable.

With regard to patients with a complete spinal cord injury, the development of more complex and sophisticated systems for grasping and subsequently for standing or walking will continue. These systems should provide a considerably higher number of stimulation channels for restoration of multi-joint movements. They should have the capability of proximal nerve stimulation or direct spinal cord stimulation with minimal invasiveness. Specific subsystems will be integrated for recording of signals from natural sensors for realization of a ''fatigue-optimal'' closed-loop stimulation. In this class of systems, with multiple degrees of freedom to be controlled, it will be very important to search for novel man-machine interfaces to interpret the patients commands. Particularly, the use of BCI for ''thought''-control of the FES seems to be an attractive alternative to traditional control methods. Recent experiments in humans with an intracortical multi-electrode array show that it is possible, in principle, to record the activity of only a few neurons and herewith control several degrees of freedom with only minimal training time [3]. A lot of research work has to be done to make the components stable for long-term application; this is the most crucial prerequisite for regular clinical use. Furthermore, it is very important to conduct an open discussion on the ethical issues and the risks of damaging an intact brain with this highly invasive technique. Nevertheless, despite all concerns, this way of control seems to be the only alternative to high-lesioned patients who have no active voluntary movements for control of a neuroprosthesis. Most control methods developed in the past, e.g. using mimic or tongue movements, are not accepted by the user because of cosmetic reasons or limitations in communication. These patients are dependent on full-time care, but based on the possibilities of modern microelectronics, they can have a chance to take a big step forward on the way back to normality and an independent and self-determined life.

When carefully studying the literature, one may get the impression that a race is going on between biomedical engineers, basic biological researchers and ambitious surgeons and therapists. The clinical community is very curious about the question who of the competitors will cross first the final line. An analysis of the results of all these disciplines concerning overall functional rehabilitation leads to the conclusion that nobody will achieve the final goal of complete restoration of functions on his/her own. Experienced surgeons will stabilize the spine also in the future and additionally, they will have to apply novel drugs in the spinal cord lesion in order to enhance axonal regeneration. Basic researchers should develop new strategies or combinations of effective methods for neuroregeneration and prove their safety in animal experiments and clinical trials. Even if axonal regeneration in the spinal cord could be enhanced, it is too simple to think of growing axons contacting their former counterparts. Since the nerve fibers within the spinal cord will not be perfectly reconstructed to its prelesioned state, it is most likely that functional recovery will not be achieved to a full extent. Therefore, motivated therapists need to train the patients – probably with the help of novel, robotic training machines and support the effects of drug interventions. Finally, engineers and technicians should develop neuroprostheses that can be applied for long-term functional support of the patients in whom functions remain limited or absent despite the application of the methods described above. The key to an overall success will be a concerted action of many disciplines initiated by clinicians who are not willing to accept the very unlucky fate of such patients.

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Neural prostheses and biomedical microsystems in neurological rehabilitation

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Summary

Interfaces between electrodes and the neural system differ with respect to material and shape depending on their intended application and fabrication method. This chapter will review the different electrode designs regarding the technological implementation and fabrication process. Furthermore this book chapter will describe electrodes for interfacing the peripheral nerves like cuff, book or helix as well as electrodes for interfacing the cortex like needle arrays. The implantation method and mechanical interaction between the electrode and the nervous tissue were taken into consideration. To develop appropriate microtechnological assembling strategies that ensure proper interfacing between the tiny electrodes and microelectronics or connectors is one of the major challenges. The integration of electronics into the system helps to improve the reliability of detecting neural signals and reduces the size of the implants. Promising results with these novel electrodes will pave the road for future developments such as visual prosthetics or improved control of artificial limbs in paralyzed patients.

Keywords: Microelectrodes; recording; stimulation; array electrode; cuff electrode; book electrode; sieve electrode; intrafascicular electrode.

Introduction

For technical communication with the neural system, interfaces are needed to transform the biological signals into technical signals. The basic components for these interfaces are electrodes that transform the ion current of the biological system into the electrode current of the technical system and vice versa. Several requirements must be fulfilled for this purpose. The basic requirement for all components intended for direct interaction with the human body is the biocompatibility of the used material. For any medical stimulation electrodes, the biocompatibility must also be established under stimulation conditions. Beside the *biochemical* biocompatibility of the implants, the *mechanical* biocompatibility presents an important issue in neuroprosthetics [39]. This aspect includes any mechanical damage or irritation during application, but also during the implantation process. Fibrotic tissue is a possible reaction of the body; the insulating quality of such tissue between the electrodes and the neural tissue can reduce the quality of signal transfer. Moreover, differences between the mechanical properties of the electrodes and the neural tissue can result in an increase of stimulation thresholds in long-term applications [30]. Another requirement is the selectivity of the interface like fascicle-selective stimulation of a peripheral nerve or single neuron recording in the central neural system. Design and implantation method can influence the selectivity, as well as intelligent data analysis or stimulation pulses. For recording purposes, the design of the electrode, especially the integration of preamplification, can improve the signal-to-noise ratio and thereby the reliability of the signal recording [10]. All components of neuroprostheses must be stable with respect to function, both during implantation and for long-term application. In some cases, implantation methods are needed with a tool for the proper placement causing as little trauma to the tissue as possible [27].

The principle setup of a neuroprosthesis includes the electrode, insulation material, conductive wires, signal processing units and, in some applications, telemetric units. Electrode materials with stable electrochemical properties like electrochemical impedance and corrosion stability are required. So far, common materials for implanted electrodes have been platinum, platinum-iridium alloy, iridium, iridium-oxide, titanium-nitride and stainless steel. But new materials like conductive polymers and galvanic plated platinum are under investigation. For insulation purposes, biocompatible polymers like silicone, polyimide, PTFE, epoxies and parylene C are used

as well as silicon nitride or glass. To have a flexible as well as robust connection between the electrode and a connector or a signal-preprocessing unit, electric cables consist of stainless steel or platinum-iridium. Some of these wires have a spinal construction to increase the flexibility of the material. Alternatively, polyimide-based ribbon cables can be used. The signal processing includes preamplification, filtering and in some applications spike detection. In stimulation systems, the stimulation source can be integrated into the system itself [31]. For transcutaneous transfer of the neural signals either RF-transmission or inductive, coupled systems are used [16, 9], and in some applications infra-red signals transmit the stimulation parameters from the extracorporal system to the implanted device [31]. Variations in the set up of a neuroprosthetic device depend very much on the area and purpose of the application. Retina implants, for example, have to fulfill very high requirements regarding miniaturization and the number of channels. Interfaces to the peripheral nerve system, e.g. for control of arms or legs, have much higher requirements on mechanical robustness. To fulfill the different requirements of the different applications, different technological solutions for the electrodes were developed in the past, such as precision-fabricated silicone cochlear electrodes. For higher resolution, micro-machining techniques for defining the silicon structures were used to generate systems that have the potential to integrate electronics for signal processing or signal generation. Polymer-based, thin-film electrodes can generate more mechanically flexible solutions. New approaches include polymer electronics with a flexible polymer substrate to achieve completely flexible implants. This chapter will describe different methods and designs to fabricate miniaturized neuroprostheses.

Electrodes produced by precision-mechanics

Electrodes designed for interfacing with the nervous system can be distinguished by their invasiveness. Cuff, helix, book, epineural or intraneural electrodes, for example, are electrodes for contacting the peripheral nerve. Cuff, helix and book electrodes enclose the nerve without the need of penetrating the epineurum for fixation or placement of the electrode [1]. Using a block shaped biocompatible material with parallel trenches, several nerves can be placed separately in one *book electrode*. With a small plate the electrode can be closed. Tiny pieces of metal are inserted into each trench to contact the nerves. The most common application of these electrodes consists in implanting them within the spinal column to stimulate the nerve roots for bladder voiding in patients with spinal cord lesions [5].

Cuff-shaped electrodes enclose the nerve completely over a certain length of the nerve. Thereby the insulation material helps to concentrate the current flowing inside the cuff. This reduces the amplitude needed for stimulating the nerve and increases the amplitude of the recorded nerve signals.

Different electrode configurations inside a cuff electrode are used for recording signals from the nerve or transmitting signals to the nerve (i.e. stimulating it). A cuff electrode with one respective electrode ring distal, proximal and central of the tube is proposed for recording neural signals. By using the electrode in combination with specific amplifier configurations, this configuration allows for suppression of external noise sources, like line-interface or electrical muscle signals. The different velocities of the nerve fibers generate nerve signals with different time delays inside the cuff electrode. When more than three rings are used in one cuff, velocity-selective recording is postulated by post-processing of the signals [10]. On the other hand, fascicle-selective stimulation can be achieved by using a cuff electrode with several electrode sites around the nerve instead of the centre ring electrode [26]. These electrodes concentrate the stimulation current on different sites and thereby chiefly stimulate the fibers that are in direct contact with the electrode. Different mechanical solutions are used to close the cuff electrode on the nerve, e.g. a piano hinge or a spiral cuff. The spiral cuff automatically closes around the nerve by virtue of its construction. For the piano-hinge closing mechanism, an additional seal has to be included. In all cuff configurations, compression of the nerve must be avoided. Therefore the diameter of the electrode must be larger than the diameter of the nerve, at least for long-term implantation purposes [1]. An alternative concept consists in a *flat-nerve electrode* similar to a cuff, but with a flat-cross section. By flattening the nerve, the fascicles become more separated so that a more selective stimulation and recording becomes possible [36], thus facilitating subfascicular selective stimulation. To prevent damage to the nerve, the cross-cut area of the electrode must be larger than the cross-cut area of the nerve. By this method an intensive electrode-nerve contact without compression of the nerve can be achieved. *Spiral electrodes* are based on the same concept as cuff electrodes, which is to place the electrode inside electrical insulating material. In contrast to the cuff electrodes, however,

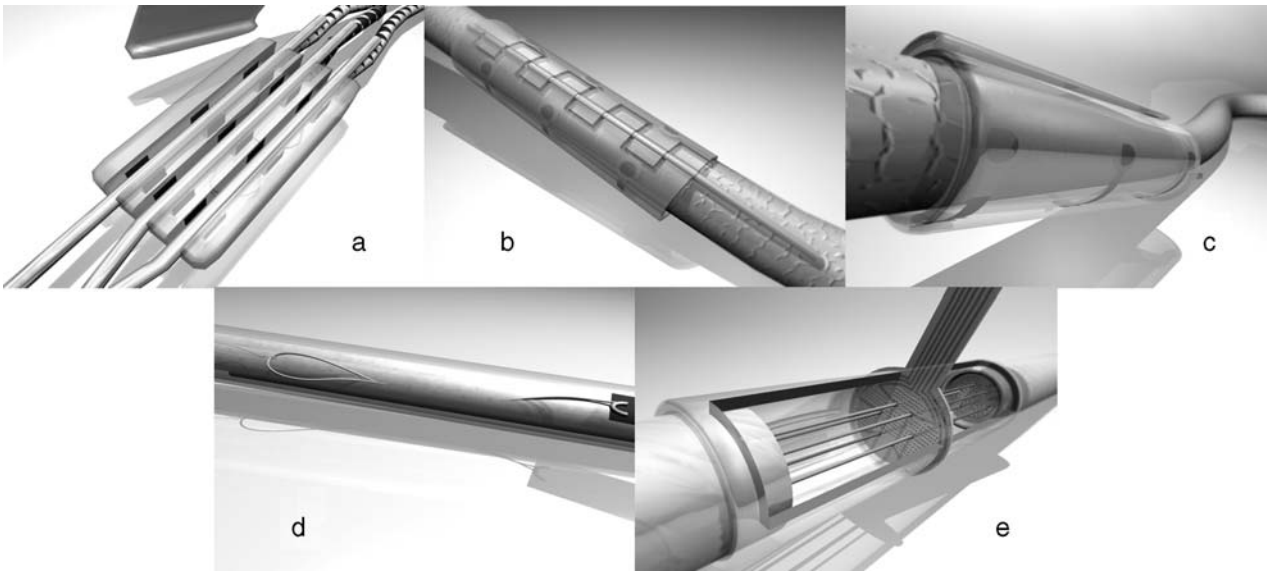

Fig. 1. Implantation of electrodes at peripheral nerves: (a) book electrode, (b) cuff electrode (piano hinge) (c) cuff electrode (spiral) (d) intrafascicular electrode (e) sieve electrode (FhG-IBMT, Germany)

the shape of the insulation material is like a spring. This mainly affects the implantation method. Suture included into the spiral electrode, emerging at the end of the spiral, can be used to open the electrode and to wrap it around the nerve. Different kinds of configurations with two, three or more spirals combined into one electrode have been developed. One of the clinical applications is the stimulation of the vagus nerve for treatment of epileptic disease [7, 11].

All of the electrodes described above can be placed around the nerve in a less invasive way, without penetrating the epineurum. Epineural electrodes designed like tiny wire loops are sutured more invasively to the nerve to stabilize the position of the electrode at the peripheral nerve [19]. Other implantation sites like the spinal cord need no direct fixation of the electrode to the nervous tissue. The electrode can then be fixed to other tissue because the body movement in the direct vicinity of the spinal cord is less tangible than near the peripheral nerves. Therefore the electrode construction needs no direct fixation. Ring shape electrodes are placed in longitudinal direction on a wire construction that can be placed epidurally for stimulation of the spinal cord. This kind of electrode can also be used for deep-brain stimulation by inserting the electrodes into the cortex through a hole in the skull bone. An alternative design of epidural electrodes consists in disc shape electrodes placed in a flat silicone foil. Extending this construction to an array of electrodes enables cortical mapping by placing the electrode array on the cortex of the patient. For this approach the foil, including the electrodes, has to be flexible to adjust to the shape of the cortex.

In analogy to tungsten needles injected into the nerve for neurophysiological acute experiments, wire-like electrodes to be sutured directly via the fascicles of a nerve have been developed. They consist of a Teflon-insulated Pt–Ir wire of 25 μm diameter with a needle at the tip for implantation. The main advantage of this kind of electrode is their high selectivity. Both highly selective recording and stimulation are possible with this kind of electrode [41, 20]. On the other hand, the number of channels is restricted by the need of a separate wire for each channel. One possibility to increase the number of channels is to place needles in an array. By using 25 μm wires as needles in an array of 4 times 6 electrodes, selective cortical activity was recorded to interpret the grip intention of a monkey. The insulated electrodes were fixed at the end by epoxy and only the tips of the electrodes were uninsulated to achieve high selectivity [35]. For stimulation of muscles a common method is used to stimulate the neural structure, which innervates the muscle, directly at the motorpoint. This allows for a robust placement of the electrode directly on the muscle with less risk of damaging the nerve. These epimysial electrodes have a disc or line shape electrode embedded in reinforced silicone for fixation. The main application consists in the stimulation of muscles of paralyzed people for functional restoration [33, 17]. Pacemaker electrodes are a special variety of this kind of electrode. Different kinds of fixation shapes like screws or barbs

Fig. 2. Cochlear electrode (Med-El, Austria)

are examples of the huge number of variations in this electrode type. Depending on the improvements in the pacemaker electronics, the requirements for these electrodes increase. Modern electrodes should combine low and stable stimulation thresholds with the possibility to record the heart response at the stimulation for close loop control of the stimulation parameters.

Electrodes designed for implantation into the cochlea present a special challenge for precision mechanics. Eight to twenty-four electrode sites are included in a longitudinal direction on a single electrode. In addition to this high number of electrode sites, the implantation method and thereby the final position of the electrode in relation to the nerve is different; self-furling designs or inner lumens in the electrode are used to insert guide wires as in pacemaker electrodes. Depending on the disease, the acoustic nerve may not be functioning. In these cases, the auditory brain stem can be stimulated directly via small arrays of electrodes, similar to those used for cortical mapping, but much smaller in scale. For the stimulation of nerve and motorpoints of muscles, glass tubes with electrodes on both sides have been designed. These implants are called BIONs (BIOnic Neurons) and include a stimulator and a telemetric system for energy and data transfer. Without further surgical intervention, a biopsy needle can be used to insert the cylindrical system with a diameter of around 2 mm [21]. The parallel use of different stimulators can be achieved by addressing up to 255 implants [32]. The energy and data transmission is realized by an inductive coupling of a large external coil with the implant coil containing a ferrite core. To evade the permanent use of an external coil, rechargeable batteries have been developed for the system.

Silicon

The rapid development of microelectronics and micromechanics create new opportunities for the development of microelectrodes including preprocessing electronics. The miniaturization enables higher resolution and more selective recordings. Integration of the amplifier electronics into the electrode reduces the length of the connection wires and thereby the risk of external noise contamination. The signal-to-noise ratio of the recorded neural signals is thus improved. In addition, miniaturized electronics can be designed to include signal preprocessing and telemetric interfaces to the neuroprostheses. Thereby it becomes possible to develop completely implantable miniaturized neuroprostheses [22]. Both sieve electrodes and needle electrodes have been developed by means of silicon technology. Sieve electrodes are used to contact the fibers of regenerating nerves. By placing the microsieve in the pathway of the regeneration, the fibers regenerate through the holes of the sieve electrode. Ring-shape electrodes around the sieve hole enable close contact to the regenerated fibers. Thus, extracellular recording and stimulation of neural electrical potentials can be achieved. To increase the number of fibers regenerated through the sieve, guidance channels in the form of tube-like silicone structures are placed on both sides of the sieve. The proximal and the distal part of a peripheral nerve can be fixed in the tube by suturing the nerve stumps into the silicone tubes. The regenerating nerve fibers will then grow proximal to distal through the sieve [38, 3]. Currently, the application of this kind of electrode is in basic investigation stage on the nerve regeneration process and models for neural signal processing. With respect to the invasive implantation of this kind of electrode, applications in humans are restricted to diseases where the nerve is disconnected. The control of prostheses for amputees is one possible future application as well as regeneration control in patients with nerves that have been disconnected by an accident [23]. While P-doped boron type $\langle 100 \rangle$ silicon wafers are used for the sieve production, a silicon-oxide mask KOH etching can be used to form pyramid wells. By etching from the rear side of the sieve, the hole size can be defined. To reduce the thickness of the silicon membrane of the sieve, a semiconductor PN-junction etch stop technique can be used to reduce the thickness of the inner part of the sieve to 10 µm [37].

In contrast to the silicon-based sieve electrodes, silicon-based needle electrodes can be inserted into the nerve tissue without cutting the nerve beforehand. By means of microtechnology, the many electrode sites can be placed on one needle, thereby increasing the number of selective recording channels. Integration of several of such needles in one electrode generates an array of contacts. This array can be placed into the nerve tissue like a comb. Needle electrodes enable placement in the peripheral and central nervous system. Using a CMOS-compatible process for the production of these electrodes, the electronics can be integrated directly into the system. In recording applications for example, the filter and multiplexer can be integrated to increase the signal

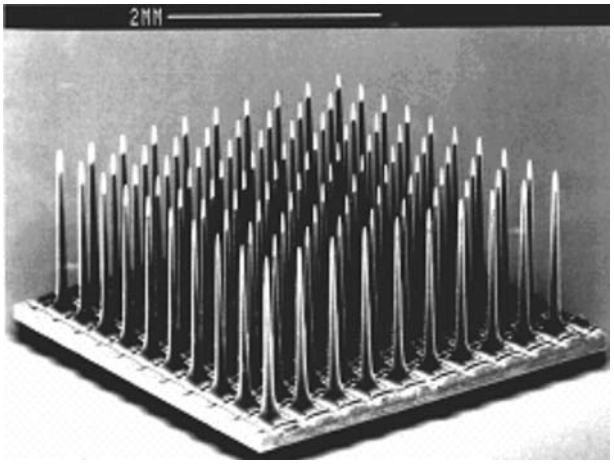

Fig. 3. Needle array electrode (University of Utah, USA)

quality [14] and to reduce the number of connection lines. Multiplexers are essentially needed for connection of a huge number of electrodes. They are all the more important when batches of such electrode arrays are combined to a three-dimensional electrode array with 256 electrodes [2]. In a stimulation approach, a stimulation unit and a telemetric unit can be integrated into the electrode structure [40]. An alternative method for construction of a microneedle array is the use of a thick silicon wafer and orthogonally cut trenches to create an array of needles. Etching of the wafer can create the final needle shape. Different array sizes can be designed by this method. For the recording of neural signals from the central neural system, a 10 times 10 array was used [8, 28]. A multilayer batch process can integrate electronics for signal processing and telemetry. By this method the technologies for the electrodes design, amplifier design and telemetry design are independent from each other. A tool for inserting the array into the tissue at high speed could perform the placement of these electrodes. For peripheral nerves a similar design of this array could be used. To contact the different fascicles of the peripheral nerves, the electrode tips must be distributed over the cross-section of the nerve. Therefore a modified design of the needle array would involve different lengths of the needles for each column of the array. When implanting the electrode alongside the nerve, thus, having the electrode run parallel to the nerve, each tip of the array would contact a separate area of the cross-section of the nerve [4].

Arrays of microelectrodes used for recording often fail after a certain period of time for several reasons. The position of the recording site in reference to neuron is critical due to the transfer function of the electrical potential of the neurons. This position can change by a micromovement of the electrodes, such as generated by acceleration during movement of free-living animals in long-term implantation. Also, degeneration of the neurons generated by the implantation of the electrode will reduce the signal amplitude. Repositioning of the neurons can compensate for some of these problems. The development of an array of microactuated microelectrodes was reported for the positioning of the recording sides. Miniaturized thermal actuators are used to manipulate each needle of the array separately. Improvements of the recording capabilities in central neural system were shown by microactuation of the needle electrodes [24]. High-precision electrodes can be produced by using micro-structuring of silicon-based substrates for recording and stimulation approaches. The advantage of integrating microelectronics into the system lies in the improvement of the signal quality. On the other hand, the substrates are rigid and the design is restricted to the process. The rigid mechanical behaviour of the electrodes also increases the risk of neural damaging or the growth of connective tissue that may reduce the interfacing properties [30].

Polyimide

The production of thin film electrodes based on photolithographic microstructuring techniques is similar to the process of structuring conductor paths in silicon-integrated circuits. As a platform for producing flexible electrodes, silicon wafers are used. They guarantee a very smooth surface and are established for use in standard microstructuring equipment. Spining of the polyimide resin on the wafer can generate the first layer of polymer. By exposure to certain temperatures, the molecules can be imidizated in nitrogen atmosphere to a 5 µm insulation layer. A layer of photoresist will be spined on the polyimide and softbacked. Photomasks are produced to expose the photoresist layer. After processing of the photoresist layer, a sputter process is employed to deposit a 300 nm thick conductive wire on the polyimide. By a subsequent lift-off process, the remaining photoresist layer, including the spare metal, will be removed in acetone. An additional metal layer to function as electrode material can be added by repeating the photolithograthic, metal deposit and lift off processes. As a surface insulation, a second 5 µm thick polyimide layer will be spined on and imidizated. Openings are required for the electrode sites and for connection of the electrodes. For this purpose and in order to generate separation

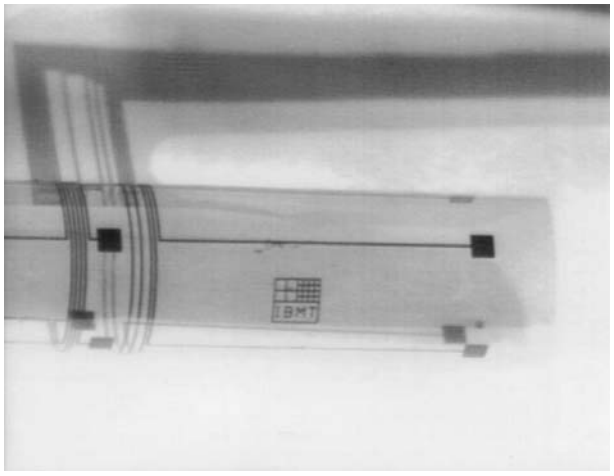

Fig. 4. Polyimide cuff electrode (FhG-IBMT, Germany)

trenches of the different structures, a reactive ion etching process in oxygen plasma can be used. To protect the rest of the polyimide, an aluminum etch mask is deposited and structured beforehand, similar to the deposition of the conductive wires and the electrodes. After the chemical removal of the aluminum layer, the electrodes can be mechanically separated from the wafer. For some applications the resulting planar structure can be used directly. For cuff electrodes, for example, a three dimensional shape of the electrode is needed. A tempering process, during which the polyimide structure is placed in a metal form, can achieve this. After the tempering, the mechanical stress in the electrode is removed, while the polyimide continues to be in the target position [34].

Similar to the silicon sieve electrodes, polyimide sieve electrodes are also used for stimulation and signal recording on peripheral nerves [25]. In difference to the silicon sieves, the polyimide electrodes include the wires for the connection of the electrodes. Moreover, additional reference electrodes can be integrated into the polyimide structure.

Polyimide cuff electrodes can be produced more precisely in comparison to silicone cuff electrodes. They are mainly needed for small nerves or a high number of electrode sites. If a more robust electrode is required, the polyimide can be combined with silicone around the cuff or for protection of the polyimide wire. Closing structures like the piano hinge or sealing can also be included through additional silicone components [18].

The restriction to a low number of electrode sites in longitudinal intrafascicular electrodes can be solved by the use of polyimide substrates. The number of electrodes can be increased by employment of microstructuring technologies [42]. Moreover, reference electrodes and ground electrodes can also be included in the substrate. The cross-section area can be reduced to 500 μm per channel. Shaft-like designs of polyimide electrodes have also been used for recording applications. Due to their flexible design, it is more complicated to insert these electrodes into the neural tissue. Therefore this approach was mainly used subdurally in the central nervous system. Arranging the electrode in an array also allows for a three-dimensional needle electrode array [29].

Similar to cochlear implants, retina implants are currently being under development to stimulate the retina where the light-sensitive cells are degenerated. In this case, a thin flexible polyimide foil can be placed on the front of the retina. Depending on the application, this system has to include the electrode as well as electronics for the stimulator, energy and signal transmission. Thereby, the entire system could be implanted into the eye [31].

Assembling technology

All systems described above require a special assembling technology ensuring optimal contact of the device to the recording and stimulation interfaces, as well as providing biocompatible encapsulation. Cables used for the connection must achieve the requested impedance as well as the mechanical and biocompatibility requirements. For conductive material, stainless steel or platinum/iridium are commonly employed due to their mechanical properties. The number of wires included in a cable varies between one for some pacemakers to 24 for cochlear implants. Elastic properties are achieved by means of a helix shape of the wire. Employment of polyimide-based ribbon cables presents an alternative concept for connecting polyimide electrodes or silicon electrodes. In polyimide electrodes, the ribbon cable can be integrated into the design of the electrode. The thin ribbon cable can be connected to the substrate of the silicon electrodes and to ceramic adapters by means of bounding technology. The bound can be placed through a hole in the polyimide foil on the rigid silicon or ceramics substrate. The conductive ring on the top of the polyimide and the pad in the rigid substrate will be connected in one step by a simple gold bound. By this method both a mechanical and an electrical connection between the cable and the substrate can be achieved.

Finally, the contacts as well as the electronic components must be encapsulated. Different polymer encapsulations as well as glass, ceramics and metal housings are used for implantable systems. Laser-sealed glass housings

are used for BION implants [32]; ceramic housings are used for cochlear implants and stand-and-work stimulation of paraplegic patients [12, 13]. Most implants, especially pacemakers, are equipped with a titanium housing for the electronical part. A combination of titanium housing for the electronics and an epoxy encapsulation for the telemetry coils was used for a stimulator supporting the grasp function in tetraplegic patients [33]. Silicone encapsulation was only used for the covering of simple electronics and DC-current free connections [6]. For small and flexible implants, parylene C was used in combination with an outer silicon cover for retina implants [15]. Long-term stability of these multilayer polymer encapsulations must be investigated separately for each combination of materials and electrical requirements.

There are different technological approaches for contacting the neural system. Unfortunately, only a few of them are admitted, i.e. certified for use in clinical investigations in humans. The challenge for the next years will be to bring the most promising electrodes to market and to establish the developed electrodes and production methods for a range of other medical applications.

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Restoration of neurological functions by neuroprosthetic technologies: future prospects and trends towards micro-, nano-, and biohybrid systems

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Summary

Today applications of neural prostheses that successfully help patients to increase their activities of daily living and participate in social life again are quite simple implants that yield definite tissue response and are well recognized as foreign body. Latest developments in genetic engineering, nanotechnologies and materials sciences have paved the way to new scenarios towards highly complex systems to interface the human nervous system. Combinations of neural cells with microimplants promise stable biohybrid interfaces. Nanotechnology opens the door to macromolecular landscapes on implants that mimic the biologic topology and surface interaction of biologic cells. Computer sciences dream of technical cognitive systems that act and react due to knowledge-based conclusion mechanisms to a changing or adaptive environment. Different sciences start to interact and discuss the synergies when methods and paradigms from biology, computer sciences and engineering, neurosciences, psychology will be combined. They envision the era of ''converging technologies'' to completely change the understanding of science and postulate a new vision of humans. In this chapter, these research lines will be discussed on some examples as well as the societal implications and ethical questions that arise from these new opportunities.

Keywords: Neural implants; cognitive technical systems; converging technologies; biohybrid systems; microsystem; neural prostheses; nanotechnology.

Introduction

Neural Prostheses help patients improve their quality of life and their activities of daily living. They substitute motor and sensory functions to some degree and modulate responses in the central nervous system. Major applications have been introduced and discussed in the previous chapter. From a technical point of view, neural prostheses are still simple systems and are well recognized as a foreign material in the human body. Therefore, in this paragraph latest technologies will be discussed with respect to their applicability in neural prostheses and their use in the restoration of neurological functions. One major goal of research for long-term stability and functionally active implants is the improvement of the cell-material interaction and the establishment of stable interfaces for exchange of information. Research was done individually by different disciplines and exciting details discovered. Findings served as ''enabling technologies'' that are currently under discussion for many new applications. Microsystem technologies integrated sensors, actuators and microelectronics at a high degree of miniaturization. Nanotechnologies and nanosciences developed new methods for surface functionalization with spatial resolution and variability that could not be reached with conventional fabrication methods so far. Biotechnology and genetic engineering led to ''hybrid'' approaches that combine biological cells with technical substrates before establishing a stable interface in the body. Each discipline is very complex and many details are not yet solved. However, disciplines have often worked in parallel and the question is how to bring their knowledge together. Some aspects of technological possibilities will be presented in the following paragraphs. Exemplary highlights in the different research fields are introduced that might lead to new research lines and fields. And last, some social and ethical implications will be discussed that will arise when new technologies are used that promise the enhancement and augmentation of human beings in latest research programs.

Biohybrid systems

Biohybrid systems summarize research approaches that combine biological cells with technical substrates. The

objective of this research is to "biologise" the interface to obtain more stable transducer properties with specified connections to the cells. Nerve–nerve interconnections shall be established in the human body instead of rather unspecific contacts at large technical interfaces. So far, fundamental research has been conducted. Only in vitro systems – so called multielectrode arrays (MEA) – have been standardized to some extent and have become a powerful tool in neuroscience for investigations on cell-cell interactions or signal transduction in brain slices.

In vitro approaches

Many investigations have been performed in the last 20 years to couple single nerve cells or nerve cell networks to technical recording equipment via electrodes or electronic components. A multiplicity of micromachined neuron probes is described in the literature [14, 20]. The structure's topology, e.g. the width of grooves to guide axons, has an important impact on the growth of the cultivated cells. Fromherz *et al.* could demonstrate current-free measurements of the membrane potential of a single neuron of a leech, a so-called retzius cell by direct coupling to the gate of a field effect transistor (FET) [3]. Using an array of FET's, a multielectrode array for a network of cultivated neurons is possible, in principle. Usually, capacitive titanium nitride or metal electrodes are used for a bidirectional information exchange with nerve cell cultures for recording and stimulation. FETs are not suitable for nerve cell stimulation; additionally, some groups reported a significantly higher amount of noise with the FET approach compared to "simple" metal electrodes. Autonomous signals, generated from cultivated neural networks without forcing them into predefined surface topologies could also be examined [4]. They were used for qualitative and quantitative drug detection. Having surface topologies on the substrate, axonal outgrowth of embryonic nerve cells from rats were observed and electrical activity was recorded [6]. These approaches were not commonly intended for transferral into implantable biohybrid interfaces.

In vivo approaches to interface the central nervous system

The use of cells in combination with microstructures for chronic implantation could only be successful, if the cells remain stable on or in the technical device and migration of the host cells can be prevented. In some investigations, silicon micromachining was used to create wells with gold electrodes on the bottom and a grillwork at the top [23]. The cells were seeded into the wells. The grillwork prevented the neurons from migration. The group of Jerry Pine managed to plant single hippocampus cells of the rat into a three-dimensional silicon structure, which was termed "cultured neuron probe" [16]. They could demonstrate that the transplanted cells inside the micro-compartments retain their capacity for axonal outgrowth. Nerve action potentials were directly recorded extracellularly from the soma of cells. However, transfer of the cultured cells from the in vitro environment into the brain remained difficult. Another biohybrid interface was introduced as "cone electrode" [8]. It combines neural regeneration with a standard wire recording technique for long-term applications. The electrode consists of an insulated gold wire fixed inside a hollow glass cone. A piece of sciatic nerve was placed in the glass cone before implantation in the cortex of rat. Cortical neurites grew into the sciatic nerve in the cone from surrounding neurons and their electrical activity was recorded via the wire in the cone. Activity of both single and multi units has been recorded for up to 15 months in monkeys [9]. The authors state the unique opportunities of the cone electrode for fundamental neuroscientific studies and for accessing the central nervous systems of patients with severe paralysis and communicative disorders. This approach has been commercialized recently (Neural Signals Inc, Atlanta, GA, USA).

In vivo approaches to interface the peripheral nervous system

In the peripheral nervous system, biohybrid interfaces are in a very early and experimental stage. A traumatic lesion of a peripheral nerve causes paralysis and leads to degeneration of the distal nerve stump by Wallerian degeneration. Healing of such a lesion occurs only under favorable conditions and involves outgrowth of axons from the proximal nerve stump, sprouting along the distal nerve stump as a guidance structure and reinnervation of the target muscles. Mostly, healing is not successful, if the lesion site is very proximal. As a consequence, alteration on the muscles in the course of atrophy prevents a formation of new neuromuscular junctions at a later point of time, when regenerating nerve fibers reach the muscle. As a result from all processes, a flaccid paralysis occurs with muscle atrophy and electrophysiological changes in muscle membrane excitability. So far, no clinical treatment or therapy can help those patients. Success has been reported in the development of an animal model

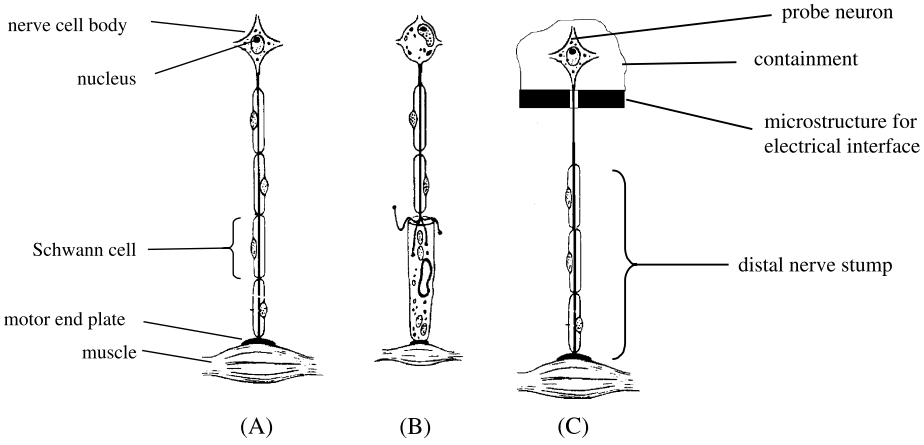

Fig. 1. Wallerian degradation following peripheral nerve damage: destruction of the myelin sheath distal to the lesion site prevents the reinnervation of the peripheral nerve and the target muscle. Neuromuscular interface at the end plate region will be destroyed. (A) Intact neuromuscular junction, (B) Wallerian degeneration [10], (C) biohybrid approach for skeletal muscle restoration [21]

to cure flaccid paralysis in a peripheral nerve with a biohybrid approach (Fig. 1). Embryonic spinal cord cells have been transplanted into a containment adapted to the distal nerve stump to restore skeletal muscle function [7, 11, 24] in an animal model of the rat. The containment consisted of a 10 mm piece of autologous femoral vein [7] sutured microsurgically to the distal stump. Fetal spinal cord was fragmented and injected into that vein containment. The proximal end of the vein containment was closed with surgical sutures. After 3–6 months, reinnervation of the gastrocnemic and tibial muscle via the distal stump of the sciatic nerve was observed, although there was no communication with the central nervous system.

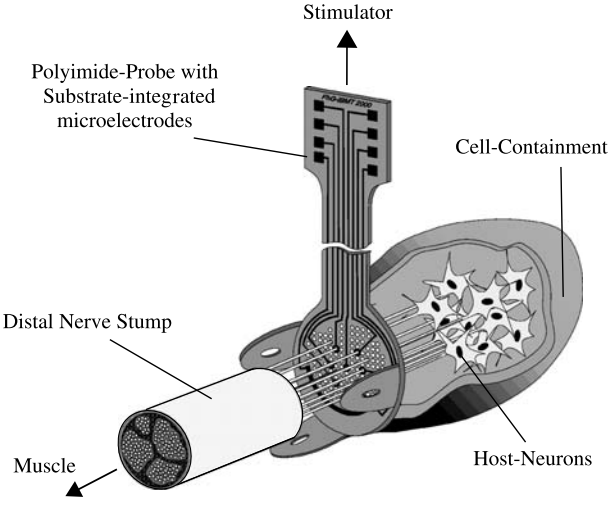

Fig. 2. Schematic view of the for neuron microprobe: biohybrid approach of a microsystem combined with motor neurons as implant after peripheral nerve damage to preserve neuromuscular junctions [21]

A micromachined sieve electrode was introduced as biohybrid interface [21] between the sprouting embryonic neurons and the peripheral nerve to allow neural stimulation for controlled muscle excitation (Fig. 2) to prevent atrophy and restore some function, e.g. in grasp after upper limp flaccid paralysis. Instead of a vein, a technical compartment was taken. The embryonic cells were purified and only motor neurons were injected into the containment. Functional regeneration was proven but the number of surviving cells tremendously decreased. Further fundamental investigations are necessary to obtain long term survival of a sufficiently high number of transplanted cells. One approach could be genetic engineering by transfection of certain vector constructs to increase the cell stress resistivity (see paragraph below). This might help the cells to survive the first 72 hours that seems to be the critical time period. Finally, the issue of using cells and their origin should be scientifically and ethically addressed at a very early point of time to develop strategies to transfer results from animal experiments into human patients. Due to latest research results, autologous adult stem cells might be favorable to prevent foreign body reactions and to overcome the crucial ethical issues whether embryonic stem cells might be a solution ethically far out of discussion.

Genetic engineering of cells within biohybrid systems

Transplantation of neuronal cells into technical compartments exhibits significant stress on these cells. Apoptosis occurs and only few cells survive. Genetic engineering might be an approach to transiently increase the cell stress resistivity. The survival rate as well as an increased

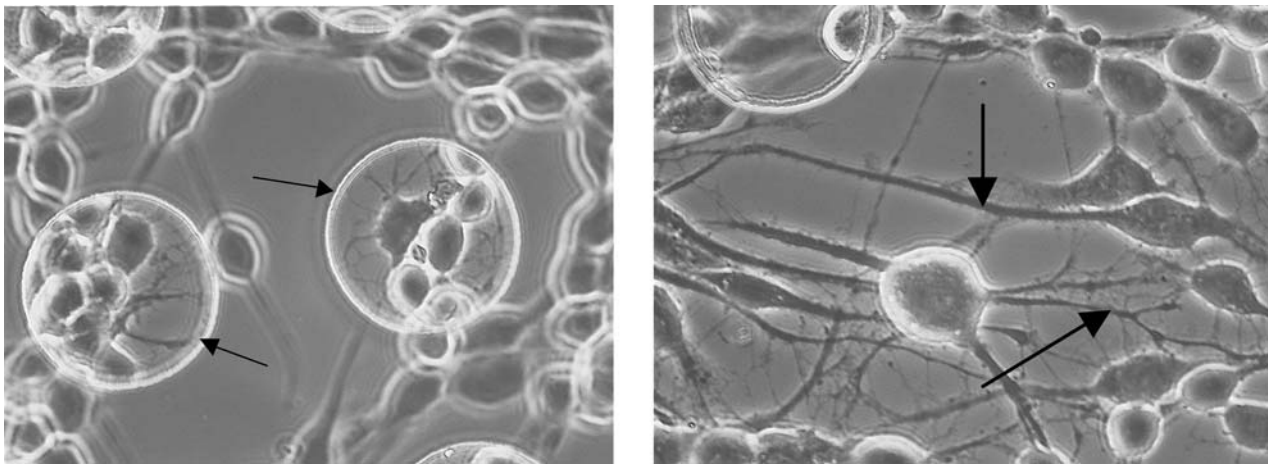

Fig. 3. Genetically modified oligodendroglia cells (cell line OLN 93) on polyimide substrate (Pyralin PI 2611, HD Microsystems); anchoring of cells (arrows) in etched via holes after $AChE_{Sense}$ transfection (left), increased neurite outgrowth (arrows) after Netrin $1_{Antisense}$ fransfection (right). Hole diameter: 40 µm [2]

proliferation was investigated in an in vitro system that was established with the oligodendroglia cell line OLN 93 [2]. The cells were genetically modified to increase their neuroprotection. In both neuronal and glial cells, overexpression of the physiologic apoptosis inhibitors Bcl1-XL and Bcl-2 and the central cell death protein Caspase 3 led to transient inhibition. Additional transfection for overexpression of apoptosis protection factor Netrin 1, that also mediates chemoattraction and increases fiber proliferation of OLN 93 cells, was investigated. While genetically non-modified cells arranged in loose cell networks on polyimide substrates, transfected cells ($AChE_{Sense}$ transfection) selectively adhered within the via holes of the sieve electrodes (Fig. 3, left). Cells with Netrin $1_{Antisense}$ transfection showed strong neurite outgrowth (Fig. 3, right) and formation of cell–cell contacts [2]. These preliminary results have to be transformed into in vivo studies for validation but give an insight into possibilities of genetic engineering within neuroprosthetic technologies.

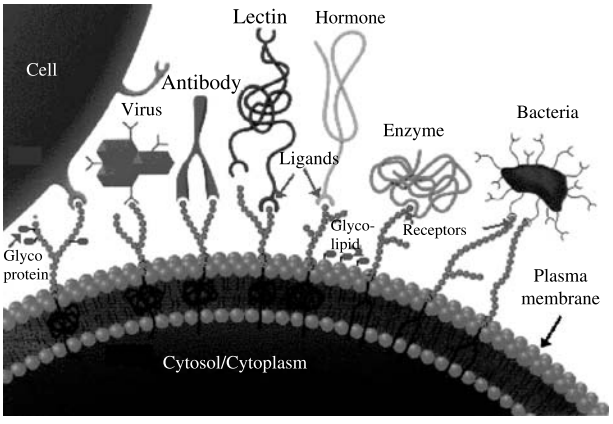

Fig. 4. Schematic view of surface modifications to promote specific cell-material interactions

Nanosciences and nanotechnology

Natural and engineering science developed new technologies to advance to the nano-dimensions and obtain a new quality in material bulk and surface properties. In the scientific and also in the common language, many issues have been adopted to the nano-world, even though mechanisms have been known for a long time. Neither nanobeads that have opened higher resolution in imaging techniques and enabled new dimensions in functional imaging nor carbon nano-tubes with highly interesting conduction mechanisms and mechanical properties will be addressed here. For neuroprosthetic applications, we will focus this wide field on only few aspects of surface patterning with the objective to mimic the surface of a biological cell as close as possible (Fig. 4) and to create nanoscale macromolecular landscapes to reduce foreign body reaction and to introduce really specific cell-material interaction for active implants.

Reactions between the artificial implant surface and the cells mainly depend on the material surface properties like surface energy, functional groups and on the nanostructure of the surface [22]. The surface modifications seem to be an adequate method to enhance cell adhesion and to get a quite physiologic proliferation pattern of cells on technical substrates with long-term adhesion and high survival rate. Polyethyleneimine (PEI) and Fluorocarbon (FC)-coatings have been patterned to establish selective adhesion on the PEI and repellent

properties on the FC on cortical neural cells. Cells showed good adhesion, patterning properties and long-term survival during in vitro experiments [19]. If this method can be transferred to in vivo models has still to be proven. The coating with laminin, poly-D-Lysin (PDL) or fibronectin is an established method of surface modification in order to increase the biocompatibility of implants or substrates in contact with nerve cells and to promote axonal outgrowth. Mostly, these layers are too thick to preserve any micro- or nanostructure that has been designed in the underlaying substrate. An electrostatic layer-by-layer self-assembly technique was recently developed [1] to overcome this shortcoming. Alternating layers of laminin, PDL and fibronectin have been assembled onto silicone rubber as substrate. The bilayers of fibronectin/PDL and laminin/PDL were only 4.4 nm and 3.5 nm thick, respectively.

The stabilization of the biomaterial/tissue interface is important with respect to fixation of medical devices after implantation. Tissue transglutaminase (tTG) has been established as a novel surface adhesion protein that might have considerable potential in forming such an interface [5]. Surface functionalization of shell cross-linked nanoparticles with an oligomeric peptide sequence that have been synthetically synthesized led to cell binding interactions but transduction of the nanoparticles into the cells also occurred [12]. Applications for predefined fixation of cells onto implant surfaces are so far not described but could possibly be considered.

While the current biomaterials are essentially bulk materials or compounds with some additional coatings, research activities point towards more sophisticated surfaces for the future: optimized three-dimensional physical microarchitecture of the surface, (bio-) chemical properties of surface coatings and impregnations and the viscoelastic properties of the surfaces. The idea is that the surface might be recognized by the combined chemical and topographical part of the surface, and the viscoelastic properties. Surface micromorphology alone, also influences the interaction between tissue cells with the implanted material [13]. Apart the above mentioned aspects of biocompatibility, biodegradation and biofouling of microsystem materials has to be taken into account [25]. Biodegradation of polymers in vivo not only limits the lifetime of the implanted material but also induces inflammatory reaction. Therefore, stability aspects and patterning of thin layers as well as self-organization of surfaces with predefined properties still have to be a focus in the development of long-term stable, implantable neural prostheses.

From interdisciplinary research towards converging technologies

More and more, scientific disciplines do not develop methods and technologies alone but in interdisciplinary teams to cope with the complex contexts of their research; by fostering these collaborations with the objective to gain synergistic effects, new research fields have been ''invented'' in the last years.

Converging Technologies are envisioned as the key issue in future research. The report ''Converging Technologies for Improving Human Performance'' from the USA in 2002 [17] stated that nanotechnology, biotechnology, information technology and cognitive science (NBIC) will ''change the societal 'fabric' towards a new structure'' [17]. The four technologies will strongly interact and their integration and synergy originate from the nanoscale. The authors summarized their ideas in the following scenarios and recommendations for major research directions:

- Expanding human cognition and communication
- Improving human health and physical capabilities
- Enhancing group and societal outcomes
- National security
- Unifying science and education

The interaction of the above mentioned ''big four'' disciplines will lead large changes in science and society. The improvement of human performance through integration of technologies is the major goal of the converging technologies. The authors summarize their envisioned applications: ''Examples of payoffs may include improving work efficiency and learning, enhancing individual sensory and cognitive capabilities, revolutionary changes in healthcare, improving both individual and group creativity, highly effective communication techniques including brain-to-brain interaction, perfecting human-machine interfaces including neuromorphic engineering, sustainable and ''intelligent'' environments including neuro-ergonomics, enhancing human capabilities for defense purposes, reaching sustainable development using NBIC tools, and ameliorating the physical and cognitive decline that is common to the aging mind.''

The European Community (EC) reacted in 2004 with the report on ''Converging technologies – shaping the future of European societies'' [15]. This report is much broader with respect to the scientific disciplines that should be taken into account. The title page specifies ''Nano-Bio-Info-Cogno-Socio-Anthro-Philo-Geo-Eco-Urbo-Orbo-Macro-Micro'' sciences to shape the European knowledge based society. This definition is more open to

public discussions and public concerns and based on the ''old'' European understanding of culture. Probably the most important difference can be found in the mission statement of the EC for an ''engineering *for* the mind'' approach instead of the ''engineering *of* the mind'' approach of the USA.

The research field of *Cognitive Technical Systems* addresses devices that learn from experience, anticipate problems and act pro-actively. Therefore, technical systems have to fulfill basic requirements, e.g. perception of the environment, the acquisition and structuring of knowledge, to draw conclusions from observations, and to make decisions in real-time to control the system behavior. The computer programs have to improve their performance with their experience. Apart from the technical challenges of knowledge representation, learning paradigms and self-learning systems, psychological and social questions strongly interact with the technical realization and implementation of these systems in health care and medicine. Machines must be able to recognize emotions and to react to it, if the machine should be really adaptable to a human user. Communication must include semantics and pragmatics of visual language. Application scenarios of cognitive technical systems as tools in degenerative diseases are currently under discussion. However, it is completely unknown, how patients with dementia, for example, will react, if a machine voice will try to guide them after they have lost their way. Do they probably lose their way on purpose to have a nice talk with the machine? How to interface nervous structures with a self-learning device in a degenerative disease? Will the system be stable with respect to a defined input-output behavior or might the adaptability of the system promote changes in personality? Should neural implants help to overcome also cognitive and emotional ''defects'' and who will define what is right or wrong? There are no short and simple answers to these questions. Experts from science, medicine, law and philosophy should try to find answers and solutions together.

The implementation of some of the ideas that have been discussed above is done in medical applications which combine monitoring of (metabolic) data and personalized therapy in a single device. The combination of *thera*py and diag*nostics* is often described with the artificial term of ''theranostics''. Micro-, nano- and bio-technologies have to be combined into a system with sensors to measure multiple parameters, detect predefined patterns of parameters as insults and deliver patient specific therapy, e.g. drug release or electrical stimulation. For neuroprosthetic applications, these multimodal systems can be envisioned in epilepsy monitoring and therapy with implants that enable spatiotemporal monitoring of brain signals with localized drug delivery after early onset detection of a seizure.

Ethical and societal questions with respect to "new technologies"

Visions for emerging technologies and application scenarios are manifold and versatile in the field of neural prostheses. Systems will become more and more complex and higher cortical areas are no longer excluded from the applications. Not only medical applications but also ''life style'' implants, like personalized transponders for wireless cash remittance in bars evolve. Manufactures of computer games already work on input channels for gaze control by signals from the brain to allow more interaction between the game and the player when chasing ''the evil one''. Manipulation of the psyche by electrical stimulation could not only be used to treat severe cases of depression as it is done nowadays but also as ''party drug'' or for mass manipulation, if worst case scenarios should be proposed.

The ''enhancement'' and ''augmentation'' of human capabilities already found their way into international research programs. Scenarios discuss the enhancement of human senses by ultrasound hearing and infrared vision in the sensor pathway and the control of additional robotic limbs in the motor pathway. The enhancement of the human brain in also an old dream of mankind that has been discussed in philosophy and science fiction literature in many nuances. The hippocampus plays an important role in the memory of our brain. Technical electronic circuits that mimic the connectivity of the hippocampus are subject of intensive research. If these chips could be connected to brain structures, completely new dimension of memory might be opened.

All scientific innovations in the field of biomedical engineering arise questions concerning the benefits and the side effects and risks of the new devices and therapies. If problems occur, e.g. due to infections after implantation, there is not only a hazard for the patients but the research is also discredited and blocked for many years in this area. Neurotechnological devices to treat diseases and functional losses have to address the same questions that neuropharmacological studies normally do. These questions include the risk-benefit analysis, the knowledge of side effects, regulations for informed consent, inclusion and exclusion criteria of patients as well as reimbursement issues and many others. Special

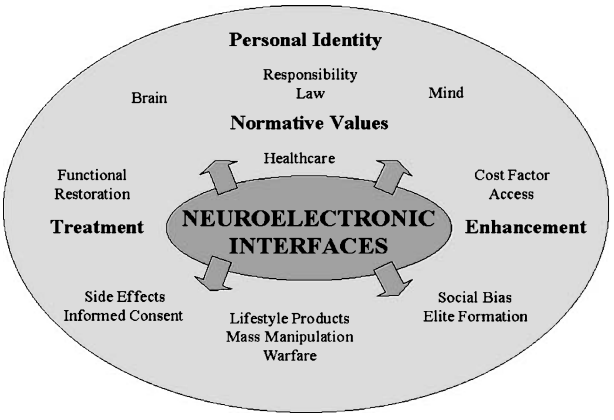

Fig. 5. Societal implications of neuro-technical interfaces with respect to ethical topics; adapted to [18]

attention should also be drawn on aspects addressing the change of personality using central nervous systems interfaces.

The real ethical challenge starts on a different level, if central nervous system interfaces are used [18]. What about implants and technologies that allow a therapy in patients and have the ''side effect'' to improve and augment the capabilities of healthy subjects? These opportunities are already in public discussion with the term ''enhancement''. The direct and possibly unintended interaction of those devices with the brain is a facet of public concern. Social imbalance due to unfair distribution or access of those augmenting implants seems also a point of public anxiety. The social and societal consequences could not be completely assessed at the present time (Fig. 5). Legal consequences of acting under the influence of a neuro-technical implant should be discussed as well as our understanding of which set of properties makes a subject member of the human race. So far, nobody can exclude that neuroprosthetic technologies and neural implants might change our complete social landscape. Therefore, the public discussion should start at an early stage, i.e. now, with adequate expertise.

Conclusions

Latest technologies have been already introduced in the neural prostheses field. They are used to solve ''old'' problems as well as to open doors to new applications and qualities to restore functions and treat symptoms after trauma or in severe diseases. Developments in neurosciences, nano- and biosciences and the use of high technological devices in daily life changed the public knowledge with respect to neural implants and the perception of human computer interfaces. Benefits of these devices become visible to larger parts of the population. However, a lot of work has to be done until a new generation of neural implants might be transferred into clinical practice. Societal implications of neural implants with respect to ethical questions appear on the horizon and should be discussed to promote useful applications and regulate and restrict misuse.

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Emerging applications

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The role of spinal cord stimulation in the management of patients with brain tumors

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Summary

High grade gliomas (HGG) have decreased blood flow resulting in hypoxia, limited access by chemotherapeutic agents, and reduced radiation-sensitivity. Spinal cord stimulation (SCS) has been used successfully in the treatment of pain and ischemic syndromes. The present article summarizes our investigations into the effects of SCS in patients with HGG. Before their scheduled radio-chemotherapy, 23 patients with HGG were assessed pre- and post-SCS using several evaluation techniques: 1) transcranial Doppler (TCD) for middle cerebral artery blood flow; 2) color Doppler for common carotid artery blood flow; 3) single photon emission computed tomography (SPECT) for tumor blood flow; 4) polarographic probe technique for tumor pO_2 measurement; 5) positron emission tomography (PET) for tumor glucose metabolism. Pre-SCS, the tumors were more ischemic and more hypoxic than healthy tissues. Post-SCS, there was significant: 1) increase in blood flow measured by TCD ($\geq$18%), color Doppler ($\geq$61%) and SPECT (15%), 2) increase in oxygenation and decrease ($\geq$45%) in percentage of hypoxic values $<$10 mmHg and $<$5 mmHg, and 3) increase (43%) in glucose metabolism. Our studies show that SCS can modify loco-regional blood flow and oxygen supply, as well as glucose-metabolism in HGG. This suggests that SCS could prove useful as an adjuvant treatment to radio-chemotherapy. These data merit further confirmatory studies.

Keywords: Brain tumors; cerebral blood flow; Doppler; glioblastoma; glucose metabolism; high grade gliomas; PET; SPECT; spinal cord stimulation; tumor hypoxia.

Introduction

Delivery of oxygen and drugs to tumors depends on regional tumor blood flow as well as on anatomical and functional abnormalities [43]. Tumor areas with hypoxia and low perfusion are resistant to radiotherapy and access to the tumor site by chemotherapeutic and radiosensitizing agents is hampered. Hypoxic, but viable, tumor cells need up to 2.5–3 times the dose of radiation as that required by aerated cells for the same radiation effect [16]. As seen in Fig. 1, the radio-sensitivity curve is asymptotic and begins to level-out above the 20–30 mmHg value. Variations in pO_2 in well-oxygenated healthy tissues will, generally, have almost no impact on radiosensitivity, whereas at a pO_2 below 10 mmHg where the radio-sensitivity curve rises exponentially, slight changes in oxygenation will have considerable consequences for radio-sensitivity. For example, it has been shown that cells with levels of pO_2 of 2–3 mmHg have twice the radio-sensitivity of cells without oxygen [17, 43]. The effect of radiotherapy is to produce ionization and excitation of atoms and molecules in the cell and to produce free radicals which mediate the radiobiological effect. Free radicals, in the presence of oxygen, can be transformed into peroxyl radicals that, often, cannot be removed by cellular anti-oxidant systems. As such, oxygen in the system is essential for the radiation to destroy tumor cells effectively [17]. Also, tumor hypoxia predisposes the cancer cells to a physiologic selection that encourages the increase in cellular variants that have lost their apoptotic potential (e.g. mutations of p53 or overexpression of the Bcl-2 genes) thus resulting in additional resistance to radiotherapy and chemotherapy [15]. Studies with xenon/computed tomography [29] or positron emission tomography (PET) [27] have demonstrated decreased blood flow in tumors, while direct measurement of pO_2 has shown low oxygenation and a high fraction of hypoxic areas at brain tumor sites [11, 35]. A measurement of tumor hypoxia can have, irrespective of tumor stage, considerable predictive value

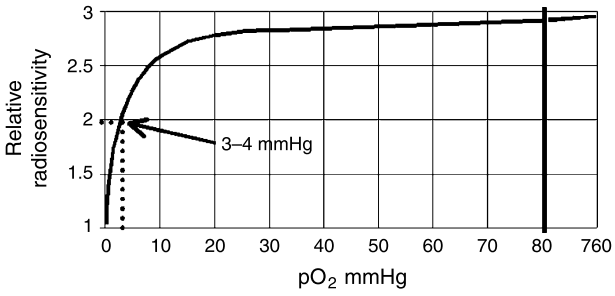

Fig. 1. Relative radio-sensitivity and tissue oxygenation; Changes in radio-sensitivity according the pO_2 levels: At low oxygenation levels, small modifications in pO_2 can produce large changes in radio-sensitivity (exponential part of the curve). At high oxygenation levels, large modifications in pO_2 lead to small changes in radio-sensitivity (asymptotic part of the curve). Modified by Clavo *et al.* [7] from the original by Hall EJ *et al.* [17]

with respect to response to radiotherapy and survival rates in patients with sarcomas [3] and tumors of head and neck [31] or uterine cervix [20]. Hence, a special Workshop of the National Cancer Institute met in 1992 to establish a consensus regarding the need to measure tumor pO_2, the methodology for this purpose (the polarographic probe method was subsequently designated the ''gold standard'') and the desirability of investigating and developing therapeutic schemes against tumor hypoxia [39]. According to the meta-analysis of Overgaard [33], modification of hypoxia can improve local control and overall survival in some tumor conditions. This would certainly be desirable in hypoxic tumors such as the high-grade astrocytomas, as has been suggested in trials using radiotherapy and hyperbaric chambers [24]. However, hyperbaric chambers have the logistic difficulty of having to be used in coordination with the radiotherapy dose administration.

On the other hand, spinal cord stimulation (SCS) is a useful technique for treatment of pain and ischemic syndromes such as vasospastic disease [36], peripheral vascular disease [6] and angina pectoris [18]. Increases in cerebral blood flow during SCS have been demonstrated by the inhaled ^{133}Xe washout technique [21], single photon emission computed tomography (SPECT) [22] transcranial Doppler (TCD) [26] and, more recently, by PET [19]. In this chapter, we summarize our studies analyzing the effects of SCS on loco-regional blood flow, oxygen supply and metabolism in patients with malignant brain tumors.

Clinical material and methods

Based on our previous studies of the effect of SCS on cerebral blood flow in non-cancer patients (unpublished data) we commenced, in 1995, to evaluate the effect of SCS in patients diagnosed as having high grade malignant brain tumors. There were 23 patients enrolled to have various assessments conducted pre- and post-SCS. For entry into the study, the patients were required to be at least 18 years of age and with a Karnofsky performance status $\geq$60%. The studies were approved by the Institutional Ethical Committee and a fully-informed consent was obtained from all patients.

Spinal cord stimulation

Neurostimulation was performed using a Medtronic system (Medtronic Neurological, Minneapolis, MN, USA). A tetrapolar electrode (Pisces-Quad®) was percutaneously inserted under local anesthesia on the dorsal surface of the spinal cord at position C2–C4, in the epidural space. An external or subcutaneous impulse generator provided an adjustable range of pulse width, intensity and frequency of stimulation. The stimulation parameters were set at a voltage of 1–3 V, pulse width of 200 microseconds and the rate at 80–100 Hz. Correct positioning and function was verified by provoking mild paresthesia in the upper limbs under test stimulation. For tumor pO_2 measurements, the SCS device was placed in position prior to surgery. Blood flow and metabolism assessment were performed after biopsy or surgery, and before commencement of the scheduled chemo-radiotherapy. Later, SCS was applied during the course of the post-surgical treatment.

Tumor pO_2 measurement

A polarographic probe system ''pO_2 Histograph 6650'' (Eppendorf GmbH, Hamburg, Germany) was used. Briefly, the probe is 0.5 mm in diameter at the shaft and 0.3 mm in diameter at the tip. The movement of the probe through the tissue is computer controlled and consists of a 1 mm forward motion and a 0.3 mm reverse motion in order to avoid tissue compression at the measurement site. In movements of 0.7 mm, the electrode can perform up to 200 measurements. Each measured value has a high spatial resolution with a sample volume encompassing approximately 100 cells. The values obtained are expressed in mmHg. The results of the measurements are automatically computed to show the mean and median values of the combined pO_2 measurements as well as the percentage of values below the 10 and 5 mmHg levels.

Three patients with pre-surgical diagnosis of high-grade brain tumor were investigated. For each patient initial, pre-neurostimulation, values of pO_2 were obtained in one healthy brain area and in two macroscopically separate tumor sites with one of them (the first) being

within the ''biopsy bed''. Neurostimulation was then activated and the measurements were repeated later in the same areas. As such, there were measurements made pre- and post-SCS in 6 tumor areas. The measurements obtained for each area studied were: 1) the median pO_2 value in mmHg; and 2) the percentage of pO_2 values <10 or <5 mmHg.

Blood flow studies

Over a period of 48 months, 15 patients with histologically-confirmed high-grade malignant brain tumors (11 at grade III and 4 at grade IV) were recruited for blood flow studies. They were 10 males and 5 females, aged between 26 and 73 years (mean: 50 years). Pre- and post-SCS, loco-regional blood flow assessments were initially performed using TCD and SPECT but, subsequently, the newer technique of common carotid volume blood flow quantification by color Doppler was incorporated into the study protocol.

Single photon emission computed tomography

SPECT measurements were conducted 10 min after intra-venous administration of 740 MBq of technetium-99m hexamethylpropylene-amine-oxime (^{99m}Tc-HMPAO). The radio-pharmaceutical agent is capable of crossing the blood-brain barrier and its intra-cranial distribution is proportional to blood flow. SPECT measurements were performed with two different devices: a Siemens Orbiter tomocamera located at the Insular Hospital (Las Palmas, Spain) and an Elscint Helix double-head 75 tomocamera located at the DIMEC center (Las Palmas, Spain). The mode of image acquisition was the ''step-and-shoot'' system with a 64×64 matrix. Measurements with both systems were in sections in parallel to the reference plane with 2 pixel thickness. Regions-of-interest were identified in the standard manner and included 3×3 pixels of cerebellum, tumor area (or tumor bed in the case of total resection), healthy contra-lateral area (the same anatomical area of the cerebral hemisphere opposite to the tumor area) and peri-tumor area (peripheral cerebral zone around the tumor area). Semi-quantitative indices were obtained in these areas using the cerebellum as reference. After the baseline SPECT measurement, the SCS device was turned ''on'' and the post-SCS SPECT measurements were performed 1–3 weeks later. For technical reasons during change-over from the 1st to the 2nd SPECT assessment, the SPECT analysis could not be performed in 2 patients. Hence, pre-SCS and post-SCS SPECT studies were obtained in 13 of the 15 patients.

Transcranial laser-Doppler velocimetry

TCD of the middle cerebral artery (MCA) was performed in the transtemporal approach with a 2 MHz probe from an ''Angiodine-2 – Fluo-Link 300''® device (DMS. Montpellier, France). Bilateral systolic and diastolic velocities (in cm/s) were recorded. In each patient, the TCD was performed pre-SCS and between 1 and 10 min post-SCS. Both TCD measurements were performed on the same day. In 3 of the 15 patients, locating an ultrasonic window to perform the measurement was not possible so, for this aspect of the study, only data from 12 patients were available.

Carotid volume and blood-flow quantification

This technique allows a quick and non-invasive evaluation of common carotid artery (CCA) blood flow and its quantification. It is based on time-domain processing and is performed using a Color Doppler Philips Ultrasound P-800 unit® (Philips Ultrasound DR5312 P-SD-800, California) fitted with a 7.5 MHz linear high-definition probe. In each patient, the measurements were performed on the same day pre- and between 1 and 10 min post-SCS. The mean blood flow (in ml/min) of both CCA was obtained $\geq$2 cm before the carotid bifurcation from 8 patients.

PET studies

We used a C-PET 250 device (Philips-ADAC-UGM, Philadelphia, USA) from the FOCUSCAN PET center (Madrid, Spain) to measure the levels of 18-fluoro-2-deoxyglucose (^{18}FDG). Patients were evaluated twice on the same day: in baseline conditions and following SCS. The baseline ^{18}FDG-PET study was conducted following the intravenous injection of 1.0 MBq/kg bodyweight. Images were acquired 45 min after the injection of the ^{18}FDG. The second ^{18}FDG-PET study commenced about 2 hours later. The patients switched-on the SCS device about 10 min before the i.v. injection of the second ^{18}FDG dose (2.0 MBq/kg body weight) and were instructed to keep it switched-on for the next 20–30 min. As such, the stimulation was turned off about 20 min following the injection and before the second ^{18}FDG-PET scan. Semi-quantitative measurements of the glucose uptake and metabolism in the brain were performed.

The maximum standardized uptake values (SUV_{max}) were calculated in both PET studies in regions-of-interest (ROI): tumor and peri-tumor areas defined with visual reference to a pretreatment computed tomography (CT) and/or magnetic resonance imaging (MRI). Additionally, applying this procedure, the ''maximal residual-activity'' of the first ^{18}FDG dose that, potentially, could have contributed to the increase in activity in the second scan was calculated for each patient. Complete data were obtained on 11 patients.

Statistical analyses

The SPSS 7.0 for Windows software package was used for all analyses. The distribution of data was assessed using the Kolgomorov-Smirnov test and, depending on whether the data were normally distributed or not, two-tailed parametric or non-parametric tests were applied. All p values <0.05 were considered statistically significant.

Results of clinical studies

Tumor oxygenation

Five of the six tumor areas assessed were more poorly oxygenated than the corresponding healthy brain tissue. The mean tumor pO_2 was less than half of the healthy brain tissue pO_2. The percentage of hypoxic values <10 and <5 mmHg was three times higher in tumor tissue than in healthy tissue. Post-SCS, the overall improvement in median pO_2 in the tumor sites was 90% ($p = 0.013$). In tumor tissue, there was a mean decrease in the percentage of pO_2 values <10 mmHg of 55% ($p = 0.026$) and a mean decrease in the percentage of pO_2 values <5 mmHg of 45% ($p = 0.018$) (Fig. 2). (For more details see Clavo *et al.* [7]).

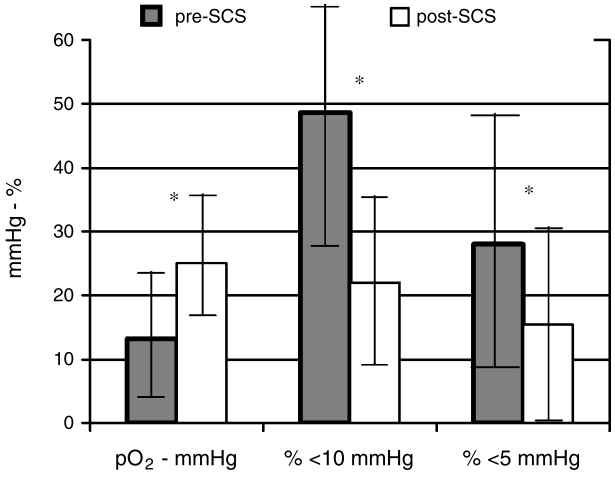

Fig. 2. Mean values of tumor pO_2 and percentage of hypoxic values: During SCS, tumor pO_2 increased 90% ($p = 0.013$). There was a 55% decrease in the percentage of pO_2 values <10 mmHg ($p = 0.026$) and a 45% decrease in the percentage of pO_2 values <5 mmHg ($p = 0.018$). Error bars show the 95% confidence intervals (from Clavo *et al.* [7])

SPECT index

Pre-SCS SPECT, the mean tumor index was 41% lower than the healthy contra-lateral index ($p < 0.001$) and 32% lower than the peri-tumor index ($p < 0.001$) which, in turn, was 13% lower than the healthy contra-lateral index ($p = 0.006$).

Post-SCS, the SPECT index increased in 75% of patients. There was a mean 15% increase in the tumor index ($p = 0.033$) without significant modification of the peri-tumor or healthy contra-lateral area indices (Fig. 3). (For more details see Clavo *et al.* [8]).

TCD measurement

Post-SCS, systolic and diastolic velocities were increased in tumor and healthy MCA in all but one of the patients. On the tumor side, systolic velocity increased by a mean of 19% ($p = 0.002$) and diastolic velocity increased by 18% ($p = 0.002$) (Fig. 4a). (For more details see Clavo *et al.* [8]).

Carotid volume blood flow quantification

Post-SCS, the mean blood flow was increased in tumor and healthy CCA in all patients. On the tumor side,

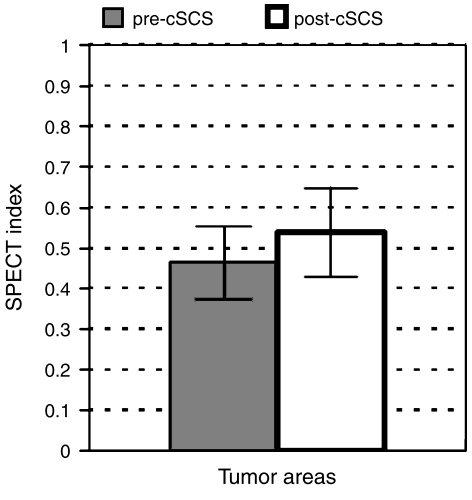

Fig. 3. SPECT indices with respect to cerebellum: During SCS, the SPECT index in tumor areas increased 15% ($p = 0.033$). Error bars show the 95% confidence interval (from Clavo *et al.* [8])

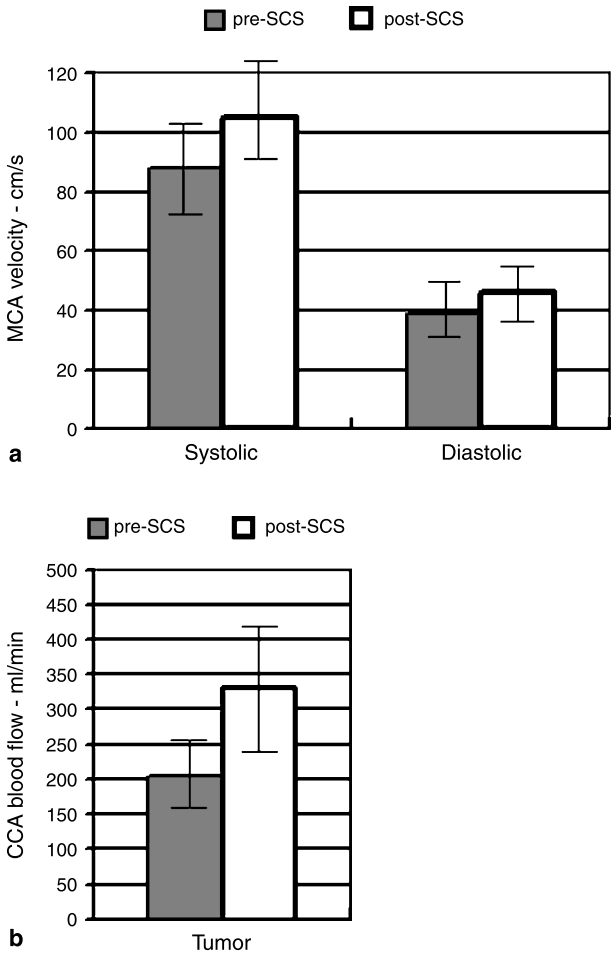

Fig. 4. Doppler studies on tumor side: (a) Doppler in the middle cerebral artery (MCA). During SCS, systolic velocity increased 19% ($p = 0.002$, *left columns*) and diastolic velocity increased 18% ($p = 0.002$, *right columns*). Error bars show the 95% confidence interval (from Clavo *et al.* [8]). (b) Doppler in the common carotid artery (CCA). During SCS, mean blood flow increased 61% ($p = 0.009$). Error bars show the 95% confidence interval (from Clavo *et al.* [8])

the mean increase was 61% ($p = 0.009$) and on the healthy side the increase was 74% ($p = 0.013$) (Fig. 4b). (For more details see Clavo *et al.* [8]).

PET results

Pre-SCS, SUV_{max} was higher in tumor than peri-tumor areas ($p = 0.048$). Post-SCS, there was a clear increase in glucose metabolism in tumor and peri-tumor areas in 75% of the patients. SUV_{max} increased 43% in tumor areas ($p = 0.035$) and 38% in peri-tumor areas ($p = 0.001$) (Fig. 5). The estimated potential "maximal residual activity" contribution (or carry-over) of the first ^{18}FDG dose to the activity observed in the second scan was $<18.5\% \pm 1\%$. (For more details see Clavo *et al.* [10]).

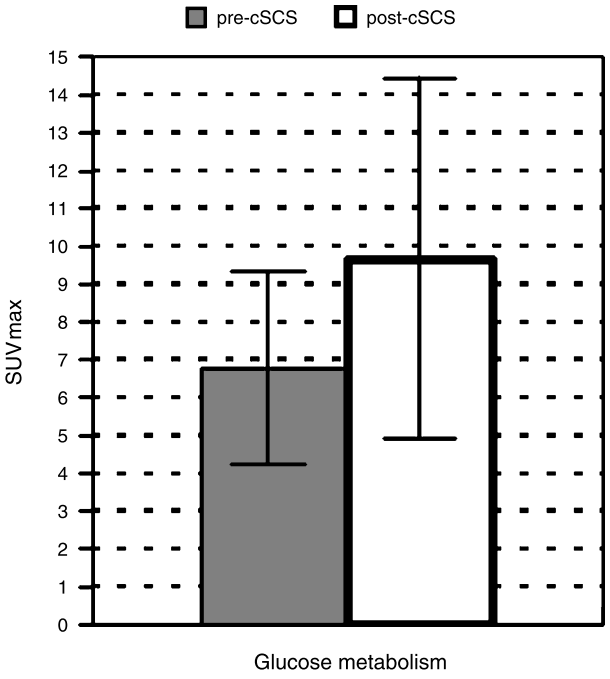

Fig. 5. Glucose metabolism in high grade gliomas: During cSCS, glucose metabolism (expressed as the maximum standardized uptake values; SUV_{max}) in brain tumor areas increased 43% ($p = 0.035$). The assessment was performed using positron emission tomography (PET). Error bars show the 95% confidence intervals. The estimated maximal residual contribution (carry-over) from the first PET study to second study was <18.5% (from Clavo *et al.* [10])

Discussion

Measurements of the changes of blood flow and oxygen supply to tumors are important objectives in cancer research since tumor areas with hypoxia and low perfusion are resistant to radiotherapy; with access by oxygen, chemotherapeutic agents and radio-sensitizing drugs are being reduced. Further, hypoxia exposes the tumor to a physiologic selection that encourages the increase in cellular variants that have lost their apoptotic potential (e.g. mutations of p53 or over-expression of the Bcl-2 genes) that result in additional resistance to radiotherapy and chemotherapy [15].

Usually, malignant brain tumors have a lower perfusion [27, 29] and a higher percentage of hypoxic areas than normal cortex [11, 35]. The basal values we have observed, in tumor blood flow and tumor oxygenation were within the range of those reported by others. As has been observed for sarcomas [3], head and neck tumors [31] and tumors of the cervix [20], hypoxia measurements could have an important predictive value, independent of tumor stage. Hypoxia is not correlated with age, gender, tumor site and/or size, arterial pO_2 or pCO_2.

Hypoxia modification is an important endpoint for cancer research [39] and these procedures can improve local tumor control and overall survival in some types of cancer patients [33]. However, radiotherapy, whether in combination with carbogen breathing or with nicotinamide, has been shown not to increase blood flow in brain tumors [23]. The favorable results obtained using irradiation of cerebral tumors in combination with hyperbaric chambers [24] are counterbalanced by the poor availability of these chambers and the logistical difficulty of coordinating their use in conjunction with radiotherapy administration within limited space and time. Hence, it is becoming increasingly necessary to evaluate new treatments that could improve the low perfusion in brain tumors in order to increase oxygen and/or drug delivery. At the same time, there is a need to diminish the vaso-constrictive effects of systemic hyperoxia produced by carbogen breathing and hyperbaric chambers.

SCS has been used to treat several ischemic syndromes and, on occasions, has been used for pain relief in cancer patients. However, there has not been any report of its use to modify ischemia-hypoxia in brain tumors. Our initial studies were implemented to test the hypothesis that SCS can increase local regional blood flow in high-grade gliomas. In the subsequent, and ongoing, studies we have used HMPAO-SPECT and TCD to assess the changes induced by SCS. Our post-SCS SPECT measurements showed a 15% tumor blood flow increase. This compares favorably with other studies using HMPAO-SPECT in which a lack of perfusion enhancement was reported following the administration of nicotinamide and carbogen in patients with glioblastomas [23]. TCD measurements following SCS in non-cancer patients had demonstrated increased blood flow velocities in MCA [26]. In our studies, patients with brain tumors also show this effect, both on the healthy side as well as on the tumor side. The increase in systolic (19%) and diastolic (18%) velocities in tumor MCA is close to the 15% increase observed in the post-SCS tumor SPECT index. These findings suggest that the tumor blood flow increases, produced by SCS, could be secondary to a decrease in the vascular resistance in the tumor area of these patients. Both, SPECT and TCD studies are relatively easy to conduct, and both suggest an increase in the local regional as well as tumor blood flow [8]. However, they have the drawback of being semi-quantitative techniques. We incorporated color Doppler assessment of CCA as a quantitative technique once this facility became available to us. This technique simultaneously evaluates velocity and vessel diameter and the data are presented as ml/min. The considerable (50%) increases in CCA blood flow shown with this technique have been described previously in animal model studies [14] both in the internal and the CCA, and are in concordance with our studies using SCS in advanced head and neck tumors [9]. However, the limitation is that CCA is at a considerable distance from the target i.e. the brain tumor tissue. Hence, we opted to try to measure the pO_2 directly in the tumor using the polarographic probe; the technique considered as the ''gold standard'' for tumor pO_2 measurements [39]. Again, the results suggested a beneficial effect of SCS; an increase in tumor oxygenation and decrease in tumor hypoxia [7]. These encouraging results would appear to quantitatively confirm the semi-quantitative results using SPECT and TCD, and are in agreement with our preliminary results with pO_2 measurements in patients with advanced head and neck tumors [9]. Since our early studies, blood flow increase has been reported by another group using CCA quantification and SPECT in patients with brain tumors [12].

On the tumor side during SCS, the rapid and consistent blood flow increases in CCA and TCD appear to be accompanied by increases in tumor blood flow and oxygenation (further explanations are proposed later). However, on the healthy side, similar blood flow increases in CCA and TCD were not followed by SPECT indices increase in these healthy areas. This may be due to the SPECT indices being expressed as a ratio between the area studied and the cerebellum. As such, healthy tissues with an increment similar to that in the cerebellum do not appear as variations in the SPECT indices. Additionally, the capacity of the healthy tissue for vascular self-regulation could limit the magnitude of the blood flow in the healthy tissues in comparison to the tumor tissues which have limited, or absent, self-regulatory capacities [43]. In this respect, in our pO_2 study we did not observe an increase in oxygenation of the healthy brain tissue during SCS. Indeed, in two of the three patients a significant reduction in the oxygenation of the healthy cerebral tissue was observed. Potential explanations are that: 1) the mechanisms of action of SCS are partially attenuated by anesthesia; and that 2) the high arterial pO_2 during the surgery performed in these two patients (pO_2 >200 mmHg) could have induced general and local vasoconstriction [1]. As such, in the patient in whom the arterial pO_2 was maintained within a better physiological range (120–140 mmHg), the healthy cerebral oxygenation was not diminished. Based on the shape of the

radio-sensitivity curve (Fig. 1), any moderate variation in the well-oxygenated healthy tissue (i.e. at the upper end of the asymptotic curve) would have very minor effects on the radiosensitivity. This could translate into a non-significant increase in toxicity following SCS administration. Conversely, what remains clear is that the SCS increased the tumor pO_2 and decreased the percentage of poorly oxygenated areas. As such, it is in the hypoxic tumor tissue that these modest changes induce the most marked benefit in radiosensitivity (i.e. exponential part of the curve in Fig. 1).

SCS has a low side-effect rate especially when compared with other adjuvant therapies used in oncology [5]. In our first group of patients, we observed that the external impulse generator (made available for trial use only) had a high rate of breakage of the electrical leads, or infection at the insertion site; these necessitated the removal of the electrode because of the high risk to the immuno-depressed status of these patients receiving corticosteroids [8]. These problems were resolved using subcutaneous impulse generators. The SCS device can be activated or de-activated as and when required within the patient's treatment schedule. The effects of cervical SCS are quite selective and appear to be mainly effective in the brain, head and neck and upper limbs. SCS has a segmental vascular effect, depending on the part of the spinal cord receiving the stimulus and, therefore, it shows fewer systemic effects than the use of vasoactive drugs. As such, the systemic vasodilatation with the associated potential decrease in blood pressure is circumvented. Similarly, SCS is not associated with gastrointestinal toxicity or phenytoin interaction, as has been seen to occur with other hypoxia modifiers such as nicotinamide [28, 34, 42]. Carbogen breathing and hyperbaric chambers are known to produce increases in arterial blood PO_2. However, arterial hyperoxia prolonged for more than 15–30 min can lead to an increase in peripheral vascular resistance, and a general vasoconstriction in most organs [1] as well as in tumors [13]. A decrease in cerebral blood flow secondary to hyperoxia has been documented in humans using transcranial Doppler [32] and MRI [44]. Additionally, it has been suggested that vasoconstriction from hyperoxia could be mediated by the sympathetic system [2].

The vascular effect of cervical SCS on brain tissue may be mediated by a sympathicolytic effect [21, 25, 36, 37, 41], the segmental liberation of vasoactive substances [38], and the activation of vasomotor centers in the brain stem [37], all of which have a competitive effect with CO_2 upon the mechanisms of cerebral blood flow regulation [26]. These effects of SCS augur well for its use in combination with carbogen breathing and hyperbaric chambers. The improvements are similar to that observed in pO_2 measurements (using polarographic probes) in advanced head & neck cancer patients undergoing neurostimulation and carbogen breathing in our institution (unpublished data).

The mechanisms for the increase in tumor oxygenation and tumor blood flow are not, as yet, clarified. Based on our above-mentioned studies, our hypothesis is that the increase in tumor oxygenation is secondary to a local regional blood flow increase during SCS. Perhaps, the anatomical and functional abnormalities of tumor blood flow and a defective self-regulation [43] could explain the lack of opposition to this increase in local blood flow. Conversely, pre-existing host vessels incorporated into the tumor could explain some of the tumor blood flow reaction to SCS.

Tumor cell metabolism depends on the glycolytic pathway which is not oxygen dependent but which is, essentially, dependent on glucose supply and which, in turn, is dependent on blood flow [43]. Hence, in our study, the increase in glucose uptake in tumor and peri-tumor areas after SCS would be associated with increased glucose availability, secondary to an improvement in blood flow. This is in accordance with our results showing cerebral blood flow improvements using TCD and SPECT [8]. This hypothesis is further supported by a preliminary report of PET measurements in a vegetative non-cancer patient in whom the pattern of increase in cerebral blood flow was almost the same as that of glucose uptake [30].

The observed capacity of SCS to increase glucose metabolism in tumor and peri-tumor tissues could result in a recruitment of tumor cells into a more active metabolic state and, potentially making them more sensitive to chemotherapy and radiotherapy. This hypothesis concurs with the described correlation between a higher metabolic rate of glucose and a better response to temozolomide [4]. Increased glucose metabolism resulting from SCS administration could lead to an adverse increase in lactate production and acidosis. However, tumor acidosis develops as a result, mainly, of inadequate drainage via the tumor tissue vascular supply [43]. Here, our hypothesis is that an increased loco-regional blood flow induced by SCS could decrease extra-cellular acidosis (i.e. a pH increase) with further decrease in tumor acidosis which would further enhance the activity of drugs such as temozolomide (more effective in an alkaline pH).

The estimated potential ''maximal residual activity'' of the first ^{18}FDG dose's contribution to the activity observed in the second scan was <18.5%. This means that the measured increase of 40% in tumor metabolism by SCS is not the real value. Probably, a more exact value would be around 20%. Interestingly, the percentage modification described in this ^{18}FDG-PET study [10] is similar to that described in our previous studies with trans-cranial Doppler and SPECT [8]. Similarly, the percentage of patients with clear glucose metabolism increase is similar to the percentage of patients with clear increase in tumor blood flow (assessed by SPECT) found in our previous study [8].

Finally, it is of note that our studies were not designed to evaluate survival post-surgery since the patients had been treated with different schedules of radiotherapy and different chemotherapeutic agents. However, in our latest group of patients, the treatment protocols have been rationalized and the patients are receiving radiotherapy at standard fractionation (2 Gy/day) and concurrent chemotherapy with temozolomide according to Stupp's protocol [40]. The preliminary results look promising.

Conclusions

High-grade malignant brain tumors are ischemic and poorly oxygenated and, frequently, include necrotic areas; these phenomena may limit treatment efficacy. Our studies suggest that, in brain tumor patients, cervical SCS induces increases in tumor oxygenation and reductions in tumor hypoxia. Also, SCS can increase blood flow in the CCA and MCA as well as tumor perfusion and metabolism. To the best of our knowledge, it is the first time that these effects of cervical SCS have been described in brain tumors patients. During the course of treatment of high-grade gliomas, the adjuvant use of cervical SCS could lead to increased local regional delivery of oxygen, drugs and modification of the micro-environment, with potential improvement in the efficacy of radio-chemotherapy. These clinical benefits need to be confirmed in further systematic trials.

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Dorsal column stimulation for persistent vegetative state

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Summary

Dorsal column stimulation (DCS) is described as a therapy for persistent deterioration of consciousness. The mechanism of its effect has not yet been elucidated. Various other methods, such as deep brain stimulation of the CM-p f complex, vagus nerve stimulation, and musical functional therapy, are being investigated as potential treatments of this problem. We present our series of DCS for persistent vegetative state and review the potential mechanisms of action and the relevant literature.

Keywords: Neuromodulation; dorsal column; stimulation; persistent vegetative state.

Introduction

Marked progress in medical techniques in the fields of emergency medicine and neurosurgery has improved the survival rate of patients with severe cerebral disorders. Although lives are saved, the incidence of persistent deterioration of consciousness, i.e. persistent vegetative state, seems to have increased. Such cases are transferred to rehabilitation departments or related hospitals where frequently substantially less care and attention is offered to them compared to the acute stage. Persistent deterioration of consciousness, which is not due to an acute problem, is unlikely to become the target of active rehabilitation. This condition is not actively treated as a distinct clinicopathological entity. Neurosurgeons who are very actively involved in the acute stage of patients have neglected making efforts after the patients enter the state of persistent deterioration of consciousness, regarding them not as being their therapeutic responsibility. As a result, the patients' families themselves have taken on the mental, physical, economical, and social difficulties. Such cases have not become collectively a social issue because the survival of most patients in this state is not long due to various complications. Recently, persistent deterioration of consciousness attracted public attention because: 1) the problems of quality of life (QOL) in these patients and their families remain poorly treated, 2) very high medical costs are caused by a condition which is uncertain whether it will improve, 3) very few facilities specialized in the treatment of persistent deterioration of consciousness are available, 4) euthanasia is discussed in Europe and America, and 5) new therapeutic methods, such as dorsal column stimulation (DCS), musical functional therapy, and drug therapy, which were not available in the past can now be attempted. Here, we report our studies on the efficacy of DCS for patients with persistent deterioration of consciousness and describe the surgical procedure and the stages to the decision for its application.

Deteriorated consciousness

Moruzzi and Magoun discovered in a cat study that the reticular formation extends over the lower medulla oblongata, pons, midbrain, hypothalamus, and thalamus and has projections to the cerebrum. It excites the entire cerebrum through the thalamus and, hence, this system has a big influence on arousal. They proposed the concept of the ascending reticular activating system (ARAS), which is considered to be the center of arousal [9].

The degree of deterioration of consciousness varies widely from mild confusion to coma. There are two components in any deterioration of consciousness, arousal reaction and cognitive reaction. The Glasgow Coma Scale and Japan Coma Scale are widely used by us in

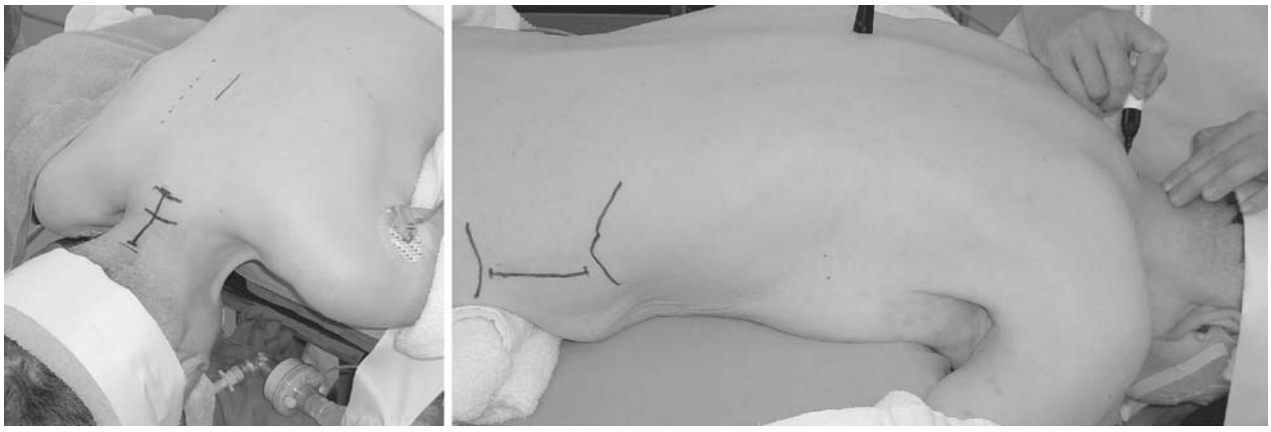

Fig. 1. Patient positioning and incision sites for the DCS procedure

order to evaluate the arousal state. This evaluation is based on the presence or absence of eye opening responses to various external stimulations and of verbal and motor responses to stimulations [1, 7, 8]. We use the scales established by the Japan Coma Society as indices for objective investigation of persistent deterioration of consciousness and evaluation of clinical outcomes. This method uses two scales for evaluation, a condition scale (10 items, maximum score: 10) and a reaction scale (5 items, maximum score: 20) [7, 8].

Dorsal column stimulation (DCS)

DCS has been used as a therapeutic method to control chronic pain and reduce spasticity of hemiplegia. However, in addition to the above beneficial actions, we have noticed obvious improvements in other patient's reactions and facial expressions. It is well known that electrical stimulation changes the neurotransmitter levels and cerebral blood flow. Therefore, on the basis of these observed effects, this therapeutic method has been applied in persistent deterioration of consciousness.

Surgical procedure

The patient is placed in the prone position with the neck flexed under general anesthesia. In general, fluoroscopy under local anesthesia is sufficient for epidural electrode insertion. These patients, however, are in a state of persistent deterioration of consciousness and their cooperation is not possible. Moreover, patients cannot be placed in the appropriate position because of deformities and contractures of the cervical vertebrae; this prolongs the operation time and requires sedation drugs in many cases. We consider that the overall safety of the procedure is higher under general anesthesia. A 5-cm median incision is made in the posterior surface of the neck around the 5th cervical spinous process level (Fig. 1). After dissection of the muscles, laminectomy of the 5th cervical vertebra is performed. Electrodes are inserted in the middle of the epidural space towards the cranial side, and indwelled to the 2nd, 3rd, and 4th cervical levels. The leads are passed under the skin, and connected to the battery and receiver, which is subcutaneously implanted in the lateral abdominal region. Since the surgical stress is low and general condition is well monitored, this procedure is safe if it is performed with reasonable care. The devices (I Trel system of Medtronic Inc.) are completely implanted and there is minimal inconvenience in daily life and very small risk of infection (Figs. 2–4).

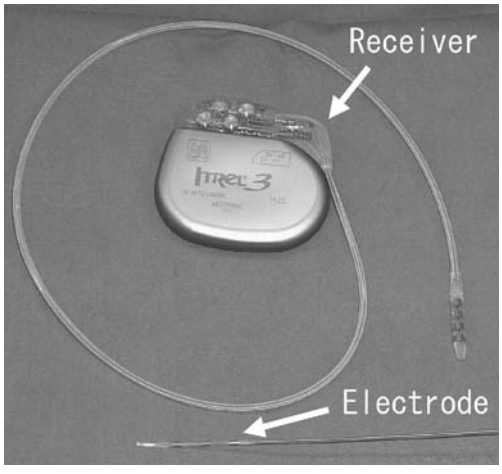

Fig. 2. The Medtronic device for DCS

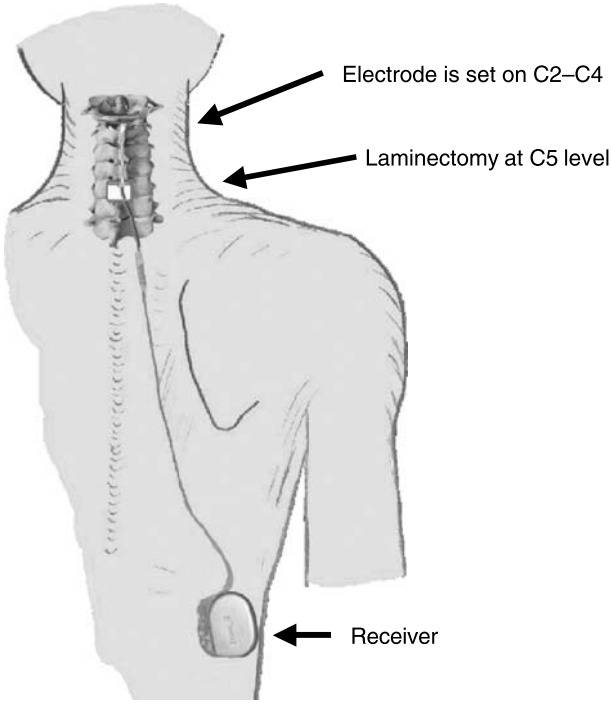

Fig. 3. Diagrammatic representation of the implantation of DCS

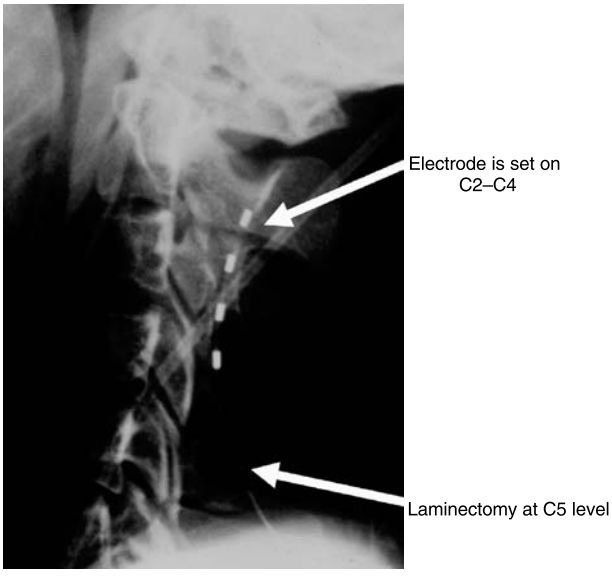

Fig. 4. Cervical X-ray demonstrating the location of the electrode for DCS. Electrodes were noted at the C2–4 levels

Electrical stimulation

If there are no complications (fever or wound problems), stimulation is initiated 3–7 days after surgery. We regard the cranial and trunk sides as the negative and positive poles, respectively, and the stimulation is offered at an amplitude of 2.0–3.0 V, rate of 70 Hz, and pulse width of 120 μsec using a cycle mode of 15-minute stimulation and 15-minute resting. This cycle is repeated in the daytime.

Mechanism of action

The mechanism of action of this method on vegetative state has not been elucidated. To our clinical and experimental knowledge, electrical stimulation increased local cerebral blood flow and the change was obvious in the cerebral cortex. On electroencephalography (EEG) during stimulation, the α waves increased and their distribution shifted to the occipital lobe and the slow waves decreased. These phenomena persisted for several hours after discontinuation of stimulation, which is the carry-over phenomenon observed in functional electrical stimulation (FES). Catecholamine metabolism in human cerebrospinal fluid was then investigated. Electrical stimulation increased NE, DOPC, DA, HVA, and 5HIAA, and decreased 3MT and 5HT. Kamei *et al.* demonstrated similar changes [6].

On the basis of such findings, it is postulated that long-term stimulation of the dorsal column provides continuous input into the pontine gracile nucleus and thalamic cuneate nucleus. Stimulation from these nuclei is transmitted to the reticular formation, the medial lemniscus, and ventral posterior nucleus of the thalamus, and disseminates to the somatic sensory area and other cortical regions. Long-term stimulation of the centromedian nucleus induces excitation of the putamen and caudate nucleus. Efferent fibers transmit to the related cerebral cortex and the most important reticular nucleus of the thalamus. These phenomena may be the action mechanism of DCS [2–5].

Preoperative examination and indications of surgery

The systemic condition is thoroughly examined before surgery. The preoperative evaluation includes: determination of the cause of persistent deterioration of consciousness, identification of the impaired area by MRI and CT, and examination of the degree of brain atrophy. Functional examination by PET and SPECT are essential because the lesions are usually diffuse. The degree of brain atrophy is marked in many cases of hypoxic encephalopathy, although the impairments associated with head injury and cerebrovascular disorder are localized in many cases. The severity of impairment may not be possible to clarify without functional imaging examination performed additionally to MRI and CT.

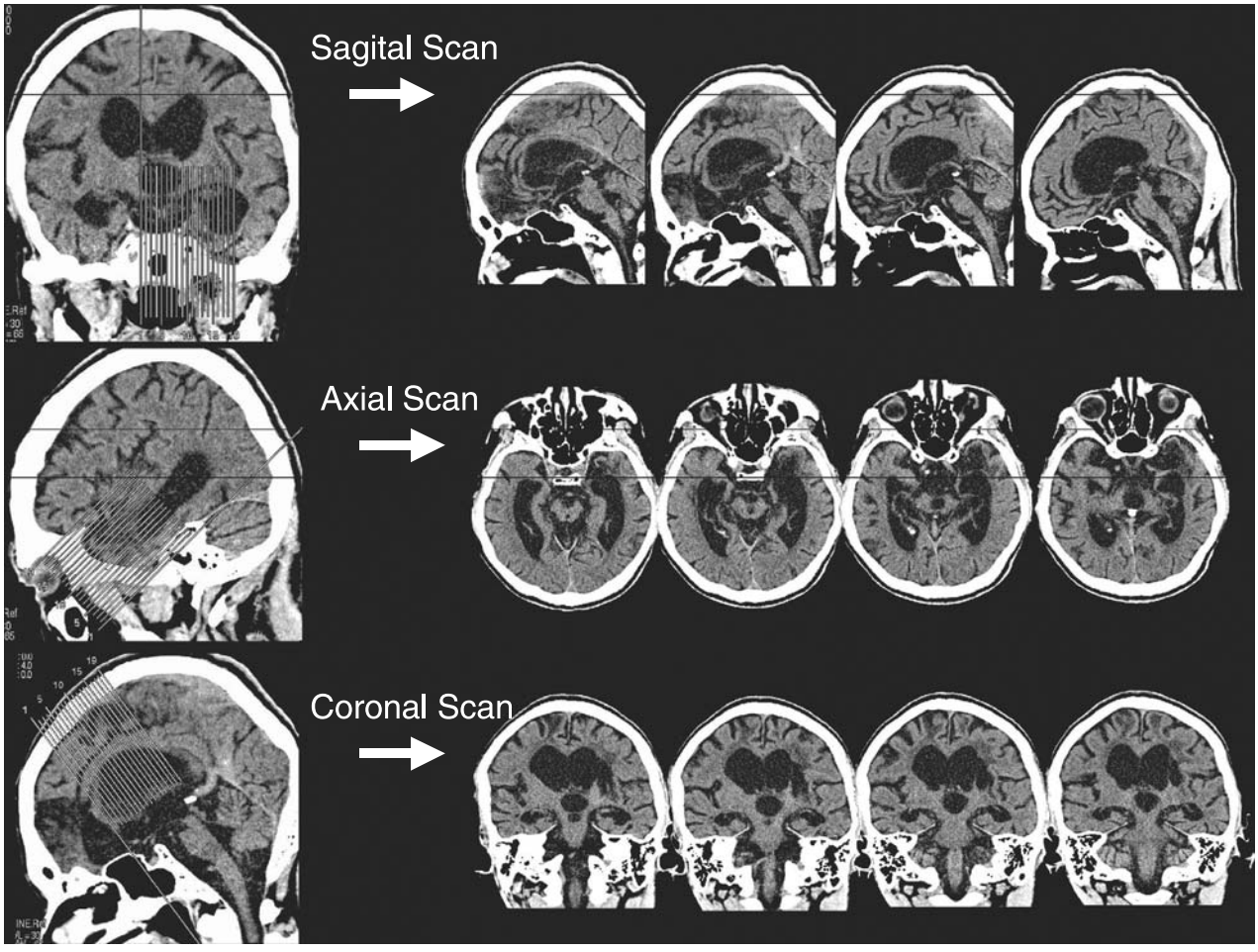

Fig. 5. Hippocampus CT in DCS preoperative evaluation

We perform 2-mm scanning of limited targets, the brainstem, midbrain, hypothalamus, hippocampus, and thalamus, using multislice CT. This hippocampus special CT is a superior method (Fig. 5); the acquisition time is about 50 sec, sedation is not necessary, and the examination can be performed after implantation of the stimulation device, although the imaging accuracy is lower than MRI. CBF is measured by SPECT using the ARG method 123I-IMP. This SPECT provides data that can be correlated with the PET data. For regions of interest (ROI) in the quantitative test, the 3-dimensional sterotaxic ROI template (3DSRT) developed by Takeuchi *et al.* is employed; PET supplements weak areas of SPECT by improving the anatomical consistency [11, 12] (Fig. 6).

We investigated indications for surgery using these tests. We have treated more than 200 patients by this method. We investigated the primary disease, age, imaging findings, and preoperative local cerebral blood flow in these patients, and noted the appearance of many common reactions to verbal orders. The indications for

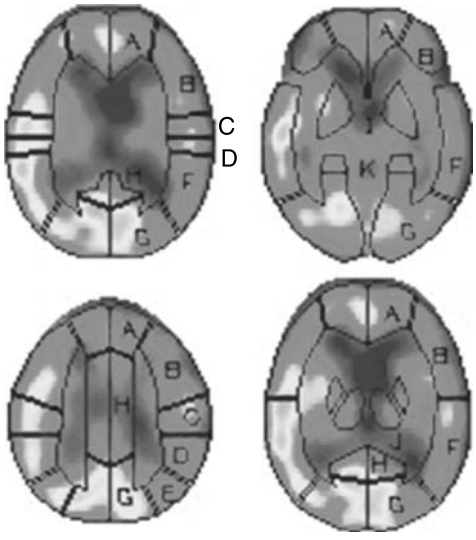

Fig. 6. SPECT image using 3DSRT. Assessment of CBF in various anatomical regions for DCS. *A* Superior frontal; *B* middle and inferior frontal; *C* primary sensorimotor; *D* parietal; *E* angular; *F* temporal; *G* occipital; *H* pericallosal; *I* lenticular nucleus; *J* thalamus; *K* hippocampus

surgery include young age, history of brain trauma, evidence of brain atrophy with no other major lesions and CBF values prior to DCS of 20 ml/100 g/min or higher. To establish valid indications, further investigation of the degree of residual brain function in patients with persistent deterioration of consciousness is necessary. Brain function is evaluated with criteria the degree and size of impaired regions, degree of brain atrophy, and degree of local blood flow. It is, however, very important to develop techniques that can identify the degree of individual residual functions [10].

Evaluation of effect

The effect of DCS is judged by the clinical improvement. However, conversion of the improvements to numerical values is difficult. Thus, we divided the degree of improvement into 'Excellent' and 'Positive'. Appearance of reactions to orders (understanding of intention), speech, and appearance of swallowing movement (oral ingestion) are judged 'Excellent'. Appearance of these means recovery from the vegetative state. Changes in expression and emotion (joy and anger, feelings) in response to stimulation, awakening, appearance of sleep rhythm, and appearance of pursuit and gaze are judged as 'Positive'. Appearance of these changes compared to the condition before DCS is recognized by the medical staff and patient's family and it is judged as 'Positive'. Based on these criteria, we evaluated the effect 1–2 years after initiation of electrical stimulation. Between 2000 and 2002, we studied 32 patients (22 males and 10 females); this patient cohort included 21 patients with trauma, 8 with hypoxic encephalopathy, and 3 with cerebrovascular disorder. On the evaluation 1–2 years after stimulation, 15 patients aged 35 years or younger satisfied the above criteria for surgery; 7 of these patients were evaluated as being 'Excellent' and 5 as 'Positive', showing that DCS was effective in 80% of these evaluated patients.

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Relationship between intrathecal baclofen and the central nervous system

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Summary

The $GABA_B$ receptor agonists display a number of pharmacological effects including central muscle relaxation, decreased self-administration of cocaine and narcotic drugs, antinociception, cognitive impairment as well as enhancement of synaptic plasticity. The main relationships between intrathecal or intracerebral baclofen and the Central Nervous System (CNS) are reviewed with particular attention to actions on pain, epilepsy and basal ganglia regulation. Since baclofen may be involved in synaptic plasticity and the development of neuronal pathways, the main issues of this field are reviewed with particular attention to the effects of baclofen on the developing brain. The role of baclofen in the regulation of movement has not been clearly understood, but recent findings support its important involvement in globus pallidus and subthalamic nucleus. The neuroprotective action of baclofen in cerebral ischemia is a matter of debate. The effects of baclofen in cognition and attention are another important issue because patients with chronic intrathecal baclofen (ITB) administration often present with impairment of cognitive functions. Drug craving and its improvement after baclofen administration is also reviewed. Finally, the clinically interesting results on the regulation of food intake and blood pressure are highlighted. The preliminary experience on the effects in cortical neuron viability at different concentrations of ITB is reported.

Keywords: Intrathecal baclofen; γ-aminobutyric acid; pain; epilepsy; neuron.

Introduction

The baclofen [β-(chorophenyl)-γ aminobutyric acid (GABA)] is a nonselective agonist ligand specific for the bicuculine-insensitive GABA receptors ($GABA_B$ receptors). The effect of baclofen is related with the balance of inhibition between neurotransmitter release including GABA, mediated by presynaptic $GABA_B$ receptors, and inhibition of neuronal excitability mediated by the postsynaptic $GABA_B$ receptors [17]. The $GABA_B$ receptor agonists display a number of pharmacological effects such as central muscle relaxation, decrease of self-administration of cocaine and narcotic drugs, antinociception, cognitive impairment, antitussive action, and inhibition of hormone release [2]. Moreover, these receptors and baclofen are involved in synaptic plasticity and the development of neuronal pathways [11]; it is known that baclofen improves conduction in demyelinated axons. It is very important to improve our knowledge of the main relationships between baclofen and the Central Nervous System (CNS). Orally administered baclofen crosses the blood-barrier poorly; hence, the study of its CNS effects should be focused on intrathecal baclofen (ITB) administration. Moreover, in animal models, baclofen has been demonstrated to be effective in the treatment of many central disorders, but side-effects prohibited a more widespread use of the oral preparation in humans. ITB, however, could provide a solution to this problem.

Role of baclofen in neurological conditions

A brief review of diseases or conditions which can be affected by baclofen is carried out with particular emphasis on possible future clinical applications.

Pain

Baclofen is known to have antinociceptive effects, yet its general efficacy as an analgesic is limited. The reason for its limited effect on pain is unknown, but it could be related to a rapid desensitization of $GABA_B$ receptors. Pain control is better in neuropathic hyperalgesia compared to inflammatory mechanical hyperalgesia [22]. A single intrathecal administration of GABA has been found to improve neuropathic pain [10] if performed within the first 1–2 weeks after injury; this effect was achieved with 250–500 ng of baclofen. The possibility

of an early ITB injection in patients suffering from neurological disease, which could be progressively complicated by neuropathic pain, should be investigated.

Epilepsy

Epilepsy may result from altered transmission of the principal inhibitory transmitter GABA in the brain. The contribution of $GABA_B$ receptor-mediated mechanisms to the generation of seizures remains unclear. Activation of $GABA_B$ receptors can exert proconvulsant effects [18]. This action is reported to develop from a block of the asynchronous GABA-mediated potential causing disinhibition and from activity-dependent changes in hippocampal network excitability [18]. On the other hand, the failure of $GABA_B$ receptor-mediated modulation of mossy fiber transmission may contribute to the development of spontaneous seizures after status epilepticus [4]. The persistent upregulation of $GABA_B$ R2 mRNA in granule cells of the hippocampus may result in the activation of compensatory anticonvulsant mechanisms [19]. In the literature, the reported cases of epilepsy in patients with chronic ITB infusion are very rare [8] and they are described in patients with either cerebral damage or aggravating factors i.e. febrile illness. Nevertheless, the possibility that baclofen could contribute to epileptogenesis remains a topic that should be investigated further.

Movement disorders

In the basal nuclei, the GABAergic neurons predominate in the striatium, globus pallidus and substantia nigra pars reticulata. GABA is the major inhibitor that regulates the neural activity of these brain regions. The role of baclofen in regulation of movement is not clearly understood, yet its actions on rat globus pallidus (GPi) as well as subthalamic nucleus (STN) have been described [5, 6] Moreover, $GABA_B$ receptors can modulate the activity of midbrain dopaminergic neurons. $GABA_B$ agonists may exert a direct effect on intracaudate circuitry rather than on glutamatergic afferents [5] Baclofen has been thought to activate presynaptic $GABA_B$ receptors on glutamate terminals, causing inhibition of glutamate release [6]. Since abnormal regulation of glutamatergic afferents has been reported to underlie the increased firing rate of neurons of the subthalamic nucleus in Parkinson disease, $GABA_B$ agonists might have a potential beneficial effect in hypokinetic disorders decreasing the release of glutamate from afferents to the STN and reducing the glutamate overflow from STN terminals in GPi and in substantia nigra. These actions on the basal nuclei could explain the results of treatment in patients suffering from supraspinal spasticity due to deep brain damage or in patients with spastic-dystonic spasticity treated by ITB.

Cerebral ischemia

Recently, the increased migration of neutrophils to the cerebral ischemic lesion after intraventricular baclofen pretreatment was reported in a rat stroke model [24]. This means that ITB could play a role in the inflammatory response and neutrophil-dependent ischemia-reperfusion injury in stroke; notably, infiltration of neutrophils to injured tissue has deleterious roles during cerebral ischemia. Yet, a neuroprotective action of high doses of baclofen has been proven [12, 14], particularly in cerebral haemorrhages [12].

Neuroplasticity

In addition to their actions in synaptic transmission, neurotransmitters play a role in establishing neuronal connections and axon growth, and as trophic factors for developing neurons. During development, GABA, the primary inhibitory transmitter of the mature brain, has an excitatory role, though the $GABA_B$ receptors can inhibit the $GABA_A$ receptors [20]. This action is found in the hypothalamus, hippocampus, spinal cord, striatum cerebellum, and cortex. In particular, $GABA_B$ agonists can stimulate retinal ganglion cell neurite outgrowth [7]; during corticogenesis in the rat CNS, cortical plate cells release GABA wich acts as chemoattractant for $GABA_B$R-containing ventricular zone neurons migrating from germinal regions [7] It might be possible that activation of $GABA_B$ Rs is necessary for proper navigation through different cortical compartments and for the acquisition of the final position in the cortical circuitry [16] On the other hand, baclofen can reduce neurite outgrowth of olfactory axons [23] through activation of $GABA_B$ receptors. These data indicate that it might be worthwhile, in patients suffering from lesions of brain or spinal cord with evidence of recovery, to consider early ITB administration. When, how, and whether this recovery will happen is a matter of investigation.

Drug craving

Baclofen has been reported to reduce in humans the craving for cocaine, heroin, alcohol, and nicotine [25].

Injections of baclofen into the ventral medial prefrontal cortex block the initiation, but not the expression, of cocaine sensitization in rats [25]; it is possible that the potential usefulness of the drug in the treatment of addiction involves $GABA_B$ receptors outside this region. ITB that acts on a wide area of CNS could be useful. Moreover, there is an inhibition of excitatory output from the medial prefrontal cortex with prevention of cocaine-induced motor activity.

Food intake

The intracerebroventricular baclofen has been found to increase food intake in the rat. The central mode of action has been proven [21] by the intracerebroventricular administration of $GABA_B$ receptor antagonist. Moreover, baclofen injection in the nucleus accumbens shell elicits an increase in food intake via a presynaptic inhibition of glutamate release [26]. In humans, improved food intake can lead to marked weight gain. In patients, the weight can also increase because of the reduction of spasticity; when calculation of calories is of critical importance, a careful surveillance of food intake and weight should be done.

Blood pressure

ITB infusion usually leads to a decrease of blood pressure and heart rate, which suggests that $GABA_B$ receptors can play an inhibitory role in the central cardiovascular regulation [3, 13]. ITB could be a method to limit excessive excitation of sympathetic pre-ganglionic neurons by substance P under noxious stimulation of primary sensory nociceptors [3]. In the literature, the clinical relevance of blood pressure and heart rate decrease in chronic ITB infusion has not been addressed. The intracerebroventricular injection of baclofen has been reported to either increase or decrease the blood pressure [27]. Baclofen injection in the nucleus of the solitary tract (NTS) increases the blood pressure [9, 27], whereas the same injection in the ventromedial hypothalamus or in rostral ventrolateral medulla produces a dose-related decrease in sympathetic nerve activity, blood pressure, and heart rate [1, 27]. In the NTS, $GABA_B$ agonists inhibit NTS neurons resulting in an inhibition of the baroflex and increase in mean arterial pressure [9]. From a clinical point of view, these actions could be very useful in patients suffering from autonomic dysfunction due to brain injury [1].

Cognitive functions

One of the effects of baclofen is memory impairment. This has been found after intracerebroventricular injection [29] and long-term administration [28]. Low doses of baclofen improved memory performance while higher doses impaired it [15]; it is important, therefore, to study long-term ITB administration to find out which is the minimum baclofen dosage that can cause memory impairment.

A first step to develop new indications for ITB administration is to study cortical neuron viability. In our Department, we have performed an analysis of cell viability by MTT colorimetric assay to determine the effects of Lioresal® and (RS)-Baclofen. Briefly, in primary neuronal culture, after 11 days, the medium was partially removed and a new plating medium containing baclofen was added. The results indicated that Lioresal®, at a concentration of 0.02 and 0.2 mg/ml, as well as (RS)-Baclofen, at a concentration of 2 and 4 mg/ml, do not affect cellular survival, neither in a concentration-dependent nor in a time-dependent manner. This means that it could be possible to administer ITB with a concentration of 4 mg/ml. Further studies are in progress to evaluate the efficacy and safety of these concentrations.

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Robot-aided rehabilitation of neural function in the upper extremities

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Summary

Repetitive movements can improve muscle strength and movement coordination in patients with neurological disorders and impairments. Robot-aided approaches can serve to enhance the rehabilitation process. They can not only improve the therapeutic outcome but also support clinical evaluation and increase the patient motivation. This chapter provides an overview of existing systems that can support the movement therapy of the upper extremities in subjects with neurological pathologies. The devices are compared with respect to technical function, clinical applicability, and clinical outcomes.

Keywords: Robotics; neurorehabilitation; movement therapy; paralysis; stroke; hemiplegics; tetraplegics; upper extremities.

Introduction

Clinical background

Arm therapy is used in neurorehabilitation for patients with paralysed upper extremities due to lesions of the central or peripheral nervous system, e.g. after stroke or spinal cord injury. The goal of the therapy is to recover motor function, improve movement coordination, learn new motion strategies (''trick movements''), and/or prevent secondary complications such as muscle atrophy, osteoporosis, and spasticity. Several studies prove that arm therapy has positive effects on the rehabilitation progress of stroke patients (see [30] for review). Many researchers compared the efficiency of different therapeutic approaches [2, 8, 25, 42]. In general, there is a positive effect on the patient's progress in rehabilitation with each therapeutic approach. However, no significant differences in the efficiencies can be found between the different approaches. Langhammer and Stanghelle [23] presented one exception, where a group of stroke patients treated with task-oriented ''Motor-Relearning-Program'' showed improved motor functions compared to another group of patients undergoing a Bobath-therapy. Besides these classical approaches, innovative therapies have been developed in recent years demonstrating distinct efficiency for specific patient subgroups. Such approaches include constrained-induced movement therapy for patients with partial functional deficits [34] as well as repetitive training techniques [10], electromyographical biofeedback [36], and functional electrical stimulation (e.g. [37]) for patients with severe arm paresis.

Several groups have observed that the longer training sessions per week and longer total training periods have a positive effect on the motor function of the arm [20, 21, 35]. In a meta-analysis comprising nine controlled studies with 1051 stroke patients, Kwakkel *et al.* [19] showed that increased training intensity yields moderate positive effects on neuromuscular function and activities of daily life (ADL). This study did not distinguish between upper and lower extremities. The finding that the rehabilitation progress depends on the training *intensity* supports the application of robot-aided therapies.

Rehabilitation robot design criteria

Robots can support the movement therapy of the lower and upper extremities. In the past, several robot-based approaches were presented to support the rehabilitation of neurologically impaired subjects. Two groups of robotic aids can be distinguished. First, there are *therapeutic systems* that are mainly used in a clinical environment, thus, being shared by several patients. The second group are *home-use systems* that assist a single patient in activities of daily living. They range from wheelchairs and mobile service robots to assistive manipulators, which can be mounted onto wheelchairs or

desks. Many of these systems were developed in the eighties and are now commercially available [22, 24, 39]. Therapeutic systems can be split into passive, active, and interactive systems. In *passive systems* no actuation is implemented to move patient limbs. Instead, limbs are passively stabilized, fixed, or limited in the range of motion. Typical technical components are stiff frames, bearings, and pulleys and ropes with counter weights. *Active systems* are equipped with electromechanical, pneumatic, hydraulic, and other drives to actively move patient limbs. The devices are either open-loop controlled or implement simple position-control strategies. *Interactive systems* are characterised not only by actuators but also by sophisticated impedance and other control strategies that allow reacting to the patient efforts. Impedance controllers are well established in the field of robotics and human-system interaction. N. Hogan first introduced them about 20 years ago [14]. The basic idea of the impedance control strategy applied to robot-aided therapies is to allow a variable deviation from a predefined leg trajectory rather than impose a rigid gait pattern. The deviation depends on the patient's effort and behavior. However, other control strategies are also possible to allow robot-patient interaction [17, 32]. Interactive systems require position and/or force sensors to measure the user-machine interaction and feed the controllers. This review article focuses mainly on interactive therapeutic systems.

Several requirements must be fulfilled when designing and applying a robot for upper extremity therapy. For example, the robot should be rather ''invisible'' so that the interaction between patient and therapist is not disturbed or destroyed. Furthermore, the robot should look and behave in a ''human-friendly'' manner [43], i.e. it should be safe, small, lightweight, ''friendly looking'', quiet, and it should be compliant, just as the therapist's hand during manual therapy. It is crucial that the robot is adapted or adaptable to the human limb in terms of segment lengths, range of motion, and the number of degrees-of-freedom (DOF). A high number of DOF allows a broad variety of movements, with many anatomical joint axes involved. Since the robot replaces the therapist's hand, sophisticated sensor systems should be integrated in order to measure the patient's muscular effort and movement. The measured data should be processed and presented to the therapist, so that she or he can assess the rehabilitation process. In general, the rehabilitation robot set-up must be rather flexible to cope with a large variety of different patients, applications and situations. It must be taken into account that the robot has to share space with additional equipment accompanying the patient (e.g., wheelchairs and respiratory equipment). Last but not least, it is fundamental to ensure that the robotic system is easy to use, because the technical background and the time of the therapist are usually limited. The modifications necessary to adjust the system to a patient must be as simple as possible.

Overview of arm robot systems

One of the first interactive robotic rehabilitation systems is the ''Hand-Object-Hand Rehabilitator'' [26]. The device consists of two vertical handles on a tabletop, each move about an axis coincident with the subject's wrist. Both handles are connected by a stick with a force transducer that measures the grasp force between the outstretched fingers of the subject's hand. A potentiometer measures the position of the hands. A motor beneath one handle can produce external torque on one hand. The motivation for this configuration was that it allows bimanual tasks, with the possibility of powered assistance for one hand. Based on the experience with the Hand-Object-Hand Rehabilitator, Lum *et al.* [27] developed a similar device called the ''Bimanual Lifting Rehabilitator''. It allows measuring and perturbing movements during the lifting of large objects, such as a cafeteria tray. The device has a handle and a force transducer for each hand attached to one rigid bar. A second bar is connected to this one through a one DOF bearing, and to a motor. The subject attempts to lift the link by the handles, without tilting it. A potentiometer connected to the bearing measures tilt, which is then regulated using a simple control law. Thus, if the object begins to tilt, the motor corrects, assisting the impaired hand. The Bimanual Lifting Rehabilitator is comprised of one active and one passive (tilt) DOF. No clinical results have been presented with either the Bimanual Lifting Rehabilitator or the Hand-Object-Hand Rehabilitator so far. However, the systems served as a basis for the Mirror Image Movement Enhancer, MIME, which was used with several patients (see below). Another interactive device is the arm trainer developed by Hesse *et al.* [12]. Here the patient has the elbow joints flexed at about 90°. Each hand grasps a handle and can be moved in one DOF. Two handle sets are available, one with a horizontal axis for forearm pronation/supination, and one with a vertical axis for wrist flexion/extension movements. The device position has to be changed depending on the selected movement. A display shows the number of cycles performed. Force and position sensors are used to enable different control modes,

including position and impedance control strategies. Another one-DOF device is the arm robot from Cozens [7]. The patient's forearm is fixed to a lever, which can rotate in the horizontal plane about an axis aligned with the elbow joint. The patient's upper arm is constrained by straps and, therefore, the device acts like an exoskeleton for the elbow joint. Interactive assistance is provided on the basis of position and acceleration signals measured by an electro-goniometer and an accelerometer. The sensor signals trigger the robot actuation as soon as a voluntary movement is being detected that is characterised by a minimum acceleration and speed. During movement a torque controller gradually changes the amount of torque applied by the robot in order to avoid transforming the exercise into a pure patient-passive manipulation.

The Haptic Master is a three DOF robot designed as haptic display by Fokker Control Systems (FCS) [38]. It has formed the basis of the GENTLE/s project supported by the European Union [11]. In this project, it is suggested to use the Haptic Master as a rehabilitation device for the training of arm movements by attaching the wrist of the patient to the end-effector of the robot. However, this set-up yields an undetermined spatial position for the elbow. Therefore, two ropes of a passive weight lifting system support the arm against gravity. The robot can be extended by a robotic wrist joint, which provides up to three additional active or passive DOF. Force and position sensors are implemented inside the robot. Interactive support for patient movements is enabled by admittance control strategies. The system has been designed for the rehabilitation of stroke patients [4]. One of the most advanced and commonly used arm therapy robots is the MIT-Manus [15], [18]. It is a planar SCARA module that provides two-dimensional movements of the patient's hand (Fig. 1). Forces and movements are transferred via a robot-mounted handle gripped by the patient. The MIT-Manus was designed to have a low intrinsic end-point impedance (i.e., it is back-drivable), with a low inertia and friction. This design feature was emphasized primarily to facilitate control of robot impedance and to ensure that the robot's intrinsic dynamics would be minimally encumbering to the patient. Force and position sensors are used to feed the impedance controllers. A three DOF module can be mounted on the end of the planar module providing additional wrist motions in three active DOF. Visual movement instructions are given by a graphical display. Clinical results with more than 100 stroke patients have been published so far [1, 9, 40, 41]. ARMin is another multi-DOF rehabilitation robot system currently being developed at the Swiss Federal University of Technology (ETH) and Balgrist University Hospital, both in Zurich (Fig. 2) [29]. The robot is fixed to the wall with the patient sitting beneath. The distal part is characterised by an exoskeleton structure, with the patient's arm placed inside an orthotic shell. The current version comprises four active DOF in order to allow elbow flexion/extension and spatial shoulder movements. Several multiple axes force sensors and four position sensors enable the robot to work in different impedance control modes. Prerequisite for some of these modes is that the robot is back-drivable. The robot is designed primarily for the rehabilitation of spinal cord injured (SCI) and stroke patients. An audiovisual display is used to allow different game modes and, thus, motivate the patients.

Based on the one-DOF bimanual training devices presented above, Lum *et al.* [28] developed the MIME

Fig. 1. Patient using the MIT-Manus [15]. (With permission from H. Krebs and N. Hogan)

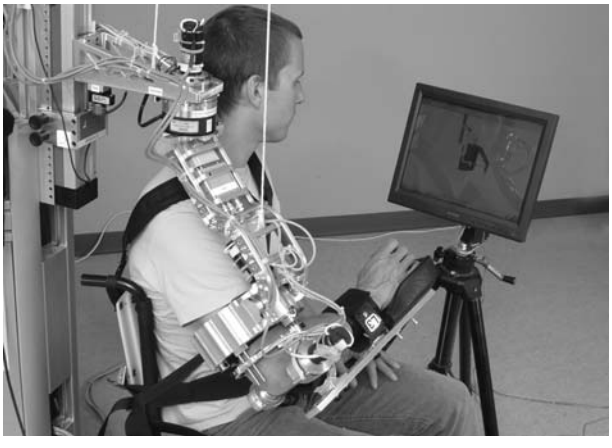

Fig. 2. Arm therapy robot ARMin including an audiovisual display

(Mirror Image Movement Enhancer) arm therapy robot. Key element of the MIME is a six DOF industrial robot manipulator (Puma 560, Stäubli Inc.) that applies forces to a patient's hand that is holding a handle connected to the end-effector of the robot. With this set-up, the forearm can be positioned within a large range of spatial positions and orientations. The affected arm performs a mirror movement of the movement defined by the intact arm. A six-axis force sensor and position sensors inside the robot allow the realisation of four different control modes, including position and impedance control strategies. In the ''bimanual mode'', the forearms are kept in mirror-symmetry by a position digitiser, which measures the movement of the intact forearm and provides coordinates for the robot motion controller. Clinical results based on 27 subjects have been published so far. Other groups propose to use devices initially designed as haptic displays for Virtual Reality (VR) applications. One of those devices is the ''Rutgers Master'', which uses four pneumatic linear actuators to provide force feedback into fingers. The Rutgers Master can be applied for the rehabilitation of hand and finger functions [3, 16, 31]. Another VR device suggested for rehabilitation of hand movement is the SPIDAR System [33]. It consists of a rigid cubic frame and several motors with pulleys attached in every corner of the frame. Strings span from each motor-pulley unit to the subject's thumb and digit finger in order to allow different finger movements and grips. With this system the subject is asked to touch and move virtual objects presented by a graphical display.

Clinical aspects

Applicability

The robot approaches applied to arm therapy fulfil the different design requirements presented in the introduction in different manners. A therapy device can be used for clinical evaluation, if recording of movement quantities such as angles, velocities, accelerations, or forces, perhaps even EMG, are possible. Thus, sensors should be integrated in the system to allow the presentation of clinical scores. Adaptability to different body sizes is easier in end-effector based systems, i.e. where the robot moves the arm by inducing forces only into the patient's hand (e.g., MIME, MIT-Manus, FCS Haptic Master, Hesse Arm Robot). In contrast, exoskeletal systems are characterised by technical joint axes that are in alignment with the anatomical axes of the patient. Thus, they are more difficult to adjust, because each robot link must be adapted to the corresponding patient segment (Cozens Arm Robot). ARMin can be considered as a mixed approach, because only the distal part is designed as an exoskeleton. The advantages of exoskeletal systems, compared to the end-effector based approaches, are that the arm posture is statically fully determined (i.e., known) and overstretching can be avoided by mechanical stops. The ease of use of a robotic system can be expressed as an inverse function of its complexity. Thus, robots with many DOF and large range of motions are more difficult and time-consuming to apply. Furthermore, operation of exoskeletal systems require more efforts during application than end-effector based approaches, because more body segments are in contact with the device resulting in more mechanical components that need to be adjusted and fixed. Other systems have the disadvantage that the patient has to put on special gloves or shells (e.g., Rutgers Master, Cozens Robot). In the FCS Haptic Master, due to the statically undetermined arrangement the arm must be supported against gravity.

Outcomes

Only a few groups working in neuro-rehabilitation robotics have published relevant clinical results so far. First results where presented by Aisen *et al.* [1]. The group used the MIT-Manus to test whether the robotic manipulation of the impaired limb is more effective than standard rehabilitation programmes. Twenty acute hemiplegic patients with a history of a single stroke and hemiplegia were selected for this study. They where enrolled in a standard rehabilitation program supplemented by either robot-aided therapy or sham robot-aided therapy. These groups were comparable in age, initial physical impairment and time between onset of the stroke and enrolment in the trial. Patients, clinical team members, and the clinical evaluator were blinded to the treatment group assignments. Standardised assessment tools where applied to measure the outcomes. Impairment and disability declined in both groups between hospital admission and discharge. The robot-treated group showed a greater degree of improvement in all three measures of motor recovery, and the change in motor status measured in the proximal upper limb musculature was significant ($p = 0.002$). No adverse events resulted from robot-assisted therapy. Subsequently, Volpe *et al.* [40] performed a similar study based on the MIT-Manus. Fifty-six patients with acute stroke and hemiparesis or hemiplegia received standard poststroke multidisciplinary rehabilitation, and were randomly assigned either to

receive robotic training or exposure to a robotic device without training (sham robot-aided therapy). Both the robot-treated and the control group had comparable clinical characteristics, lesion size and pre-treatment impairment scores. By the end of the treatment, the robot-trained group demonstrated improvement in motor outcome for the trained shoulder and elbow (Motor Power Score, $p<0.001$; Motor Status Score, $p<0.01$) that did not generalise to untrained wrist and hand. The robot-treated group also demonstrated significantly improved functional outcome (Functional Independence Measurement-Motor, $p<0.01$). Volpe concludes that robot-delivered quantitative and reproducible sensorimotor training enhanced the motor performance of the exercised shoulder and elbow. The robot-treated group also demonstrated improved functional outcome. When added to standard multidisciplinary rehabilitation, robotics provides novel therapeutic strategies that focus on impairment reduction and improved motor performance. In the latest publication of the MIT-Manus group, Fasoli *et al.* [9] showed that even *chronic* stroke patients benefit from the robotic therapy. Twenty persons diagnosed with a single, unilateral stroke occurred within the past 1–5 years, with persistent hemiparesis, participated in this study. Evaluations by a single blinded therapist revealed statistically significant gains from admission to discharge on the Fugl-Meyer Score, Motor Status Scale, and Motor Power Score ($p<0.05$). Fasoli *et al.* concluded that robotic therapy might complement other treatment approaches by reducing motor impairment in persons with moderate to severe chronic impairments [9].

Another clinical study was based on the MIME device [28]. The objective of this study was to compare the effects of robot-assisted movement training with conventional techniques for the rehabilitation of upper-limb motor function after stroke. Twenty-seven patients with chronic hemiparesis were randomly allocated to the two groups (robot and control group). All subjects received 24 one-hour sessions over two months. Subjects in the robot group practiced shoulder and elbow movements, while assisted by the robot manipulator. Subjects in the control group received conventional therapy. To evaluate patient motor capabilities, Fugl-Meyer Score was evaluated by a therapist blinded to group assignments. Compared to the control group, the robot group had larger improvements in the proximal movement portion of the Fugl-Meyer test after one month of treatment ($p<0.05$) and also after two months of treatment ($p<0.05$). The robot group had larger gains in strength ($p<0.02$) and larger increases in reach extent ($p<0.01$) after two months of treatment. At the six-month follow-up, the groups no longer differed in terms of the Fugl-Meyer test. Lum *et al.* [28] conclude that compared to conventional treatment, robot-assisted movements has advantages in terms of clinical and biomechanical measures. Further research into the use of robotic manipulation for motor rehabilitation is justified. Cozens [7] applied his robot to 10 stroke or multiple sclerosis patients aged 47–69. Each patient exhibited weakness of an upper limb, such that he or she could move the robot lever a little but was unable to complete an unassisted ten-cycle exercise with full movement range. He could show that robot assistance significantly increased the mean range of active elbow movement in every patient ($p<0.01$).

Hesse *et al.* [12] tried to determine whether use of their bilateral robotic device reduced spasticity and improved motor control in the arm of severely affected, chronic hemiparetic subjects. Twelve subjects with a period of six months since their stroke were investigated. They could maximally protract the affected shoulder, hold the extended arm, or slightly flex and extend the elbow. In 8 subjects, a significant reduction of spasticity was noticed on the Modified Ashworth Scale ($p<0.0125$) after training. However, motor control evaluated by the Rivermead Motor Assessment Score increased only minimally in 5 subjects. In another study with 44 severely affected stroke patients, Hesse *et al.* [13] showed that robot-aided arm training improved Fugl-Meyer and upper limb muscle power significantly more than EMG-initiated electrical stimulation. Coote and Stokes [6] used the Haptic Master to study the recovery of maximal voluntary isometric contractions in stroke patients. Their study consisted of 20 single case studies using different set-ups of the robotic system. Of the 20 patients who completed the trial, 13 showed a large and significant increase of voluntary muscle force. In another study, Coote *et al.* [5] showed in 19 single case studies that robot-aided therapy with the Haptic Master positively affects recovery at the level of impairment and disability.

Conclusions

This paper has presented an overview of ongoing projects, where arm rehabilitation robots are being developed and/or applied to patients. Not only technical aspects but also clinical results have been presented. Rehabilitation robots can make the therapy of upper extremity functions more efficient. The patients can train

more intensively, while releasing the therapist from manual movement therapy. Thus, the therapist can concentrate on other, more important aspects of the patient's treatment plan and/or take care of more patients. Furthermore, robotic systems provide accurate quantitative measurements of patient performance. Several clinical studies have shown the positive effects of robot-aided neuro-rehabilitation on the upper extremities. This may increase the acceptance of robotic systems applied in physical therapy. It is suggested that future systems should comprise enough DOF in order to allow arm movements within a reasonable range. This is required to perform ADL tasks and evaluate the therapeutic outcome for a broader variety of movements. Furthermore, it is expected that patient-interactive strategies will encourage and motivate the patient, thus, maximizing the therapeutic outcome. So far most clinical investigations have been limited to stroke patients. Therefore, it is recommended to develop robots and protocols that are applicable to patients with other neurological or orthopaedic pathologies such as incomplete spinal cord injury, multiple sclerosis, Parkinson's disease, cerebral palsy, arm pain as well as shoulder and elbow joint lesions.

In the future, it is important that more clinical tests are performed, in order to prove the medical relevance of robot-aided arm therapy for different patient populations. Comparisons are necessary not only between classic manual and automated robotic approaches but also between several robotic devices working with different control strategies.

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Experimental therapies for chronic pain

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Summary

Chronic pain, an underestimated but complex medical and social phenomenon, is often resistant to currently used analgesic drugs. The effect of these substances is frequently self-limiting, with increasing level of unwanted side effects caused by increased doses. Moreover, most pharmacological therapies for pain are administered systemically, either via the enteral or the parenteral route, and exert their effects on a multitude of organs and structures in the body regardless of their involvement in chronic pain pathways. Unlike pharmacological agents, biological pain therapies provide a means to target single molecules or specific types of neural cells in spatially limited areas in the central nervous system. Biological therapies utilize externally administered natural or synthetic agents acting at specific receptors on the spinal or supraspinal level, or virus or cell vectors allowing the expression and secretion of such agents in small compartments. By targeting a particular receptor or other specific protein involved in signal transmission, biological approaches to the treatment of chronic pain may provide greater analgesic efficacy without the limitations associated with current pharmacological therapies. This review summarizes published data on the most important of the currently known targets for biological therapy of chronic pain, and focuses on therapeutic approaches for modulation of these targets and on results from preclinical and clinical trials. Biological therapies for chronic pain hold great promise and are rapidly developing, but currently still are in a very early stage and therefore deemed experimental and not suitable for routine clinical use.

Keywords: Chronic pain; cell therapy; gene therapy; virus vector.

Introduction

Chronic pain is an extremely complex physiological, medical and sometimes social phenomenon with vastly different etiologies and a variety of clinical presentations. In addition to the major impact of chronic pain on activities of daily living and on quality of life of patients and their families, it represents a significant cause of human suffering, healthcare costs, and lost productivity [1, 21, 23]. In the last century, medicine and natural sciences have made great advances in the understanding of anatomical pathways and physiological mechanisms of pain perception, however still more remains to be discovered, particularly on the molecular and cellular level. Better knowledge of the fundamental genetic structure and, more importantly, of the function, dysfunction and network integration of receptors and signal transmitters involved in physiological nociception and in ''chronification'' of pain may allow us to identify specific molecules active in chronic pain and to find agents able to modulate these targets with a therapeutic intention [8, 11, 17, 18]. Chronic pain is often resistant to many of the currently available pharmacological treatments, and the action of pharmacological agents is frequently self-limiting, with increasing level of side effects caused by increased doses. Moreover, most pharmacological therapies are administered systemically, either via the enteral or the parenteral route, and exert effects on all target structures in the body regardless of their involvement in chronic pain pathways [2, 27, 30].

Unlike pharmacological pain-killing agents, biological pain therapies provide a means to target single molecules or cells in spatially limited areas in the central nervous system (CNS). Biological therapies use externally administered natural or synthetic agents acting at specific receptors on the spinal or supraspinal level, or virus vectors or genetically engineered cells allowing the expression and secretion of such agents in small and spatially limited compartments of the CNS [10, 15, 28]. By targeting a particular receptor or other specific signal-transducing protein, biological approaches to the treatment of chronic pain may provide greater analgesic efficacy without the limitations associated with current pharmacological therapies. This review summarizes the most important of the currently known targets for biological therapy of chronic pain, and focuses in some detail

on therapeutic approaches aiming at modulating these targets and on results from preclinical and, where available, from clinical trials.

Potential targets for biological therapy of pain

It seems a very difficult task to choose a single one of the many components comprising the extremely complex nociceptive network in humans, and to design an effective way of modulating the chosen target so as to decrease or abolish pain perception. As with all living structures, the degree of redundancy of systems in human nociception is high, and often blocking or activating a single receptor or non-receptor molecule is not enough to achieve sustainable and clinically useful analgesia [26, 30]. On the other hand, at least with pharmacological therapies, combinations of agents aiming at multiple targets tend to develop interactions on their own, and these interactions are often not synergistic and may negatively influence therapy outcomes [2, 8, 12]. Ideally, any given target for biological therapy of pain should have a well-known role in pain pathogenesis, a well-defined pharmacological profile with available agonists and antagonists for its manipulation, and finally it should not interfere with normal physiological processes of nociception [30]. Naturally, such ideal targets have not been identified yet, but there are potential candidate targets with more or less well defined features and properties. Such candidate targets for biological pain therapy are: opioid receptors, adrenergic receptors, neurotrophin receptors, tachykinin NK-1 receptor, protein kinase C-γ (PKCγ), vanniloid receptors (VR1), cannabinoid receptors (CB1, CB2), acetylcholine receptors (M1–M5), NMDA subtype of glutamate receptors (NR1, NR2), peripheral sodium channel (PN3), and some others [17, 18, 26, 30].

Cell therapy

Most studies of cell transplantation for pain used chromaffin cells obtained from the adrenal medulla. Chromaffin cells naturally express and release a number of neuroactive substances that are involved in the pain-processing pathways at the spinal level, including serotonin, GABA, galanin, and met-enkephalin. Injection of chromaffin cells into the lumbar subarachnoid space was shown to reduce pain-related behavior in animal models of neuropathic and inflammatory pain [3, 5, 19]. The precise mechanism of action of the chromaffin cell grafts in reducing pain-related behavior is not fully established. Chromaffin cell grafts release met-enkephalin, and the level of met-enkephalin in CSF is increased following grafting, but the grafts also elevate CSF catecholamine levels [19]. It is possible that indirect effects, such as catecholamine stimulation of inhibitory neurotransmitters from dorsal horn interneurons might account for some of the effects of the grafts [29]. Transplants of neuronal cell lines genetically modified to secrete galanin or GABA are also antinociceptive in models of chronic neuropathic pain [6]. A cell line engineered to produce and release brain-derived neurotrophic factor reduces allodynia and hyperalgesia in the chronic constriction injury model of neuropathic pain [4].

An important question in this context is how the delivery of neuroactive substances by intrathecal cell transplants does compare to the delivery of the same substances by intrathecal catheters connected to pumps. While both approaches rely on targeting of the respective agents to the distal parts of the spinal cord to minimize their effects on brain and peripheral organs, a major advantage of the cell transplant is the ability to deliver peptide neurotransmitters (e.g. met-enkephalin) in its natural conformation, even when intrathecal administration of the agents is limited by their very short half-life [4, 6, 29, 30]. The release of additional substances (such as beta-endorphin or serotonin) may add to the effectiveness of cell transplants in animal models, but on the other hand may complicate practical issues related to human treatment. In addition, the possibility of immune reaction or non-specific scar formation resulting from injection of foreign material into the subarachnoid space is not fully known. In some cases, therefore, allogeneic or xenogeneic chromaffin cells have been encapsulated in a selectively permeable polymer membrane which protects the cells from destruction by the host immune system, allows grafting without immunosuppression, and avoids intrathecal scar formation and widespread reactive fibrosis [5]. Transplantation of encapsulated bovine chromaffin cells into the subarachnoid space has been tested in 7 patients with severe chronic pain not satisfactorily managed by conventional therapy [3]. The patients received no pharmacological immunosuppression, and histological analysis, immunostaining, and analysis of secretory function all confirmed survival and biochemical function of the encapsulated cells for up to 6 months after implantation. Reduction in morphine intake and improvement in pain ratings were observed in several patients in this uncontrolled trial [3], but a controlled phase II trial has not been reported yet.

Gene therapy

The rapid development of vectors and transgene systems for somatic gene therapy has allowed these tools to be employed as experimental biological treatments for pain [10, 11, 17, 18]. One disadvantage of this approach is the inability to terminate biological activity of the expressed peptides or proteins, although this limitation may become less relevant with continued advances in the methods for control of gene delivery end gene expression [8, 17, 18, 26]. Gene therapy involves mostly transgenic peptides or proteins targeting well defined structures and specific cells in the CNS. Early experimental protocols attempted the transfer of opioid precursors genes, leading to their overexpression at the spinal level, and demonstrated proof of principle and feasibility of these approaches [10, 15]. Expression of transgenes coding for opioid peptides in primary sensory neurons or in the spinal cord induced antihyperalgesic effects in various animal models of chronic pain [11, 12]. However, numerous other molecules involved in pain processing or associated with chronic pain were identified meanwhile [13, 14], and transgene-based techniques might be particularly suitable for the evaluation of the possible therapeutic relevance of these new potential targets [30].

Neurotrophic factors are highly potent macromolecules and represent another class of biological agents with analgesic effects. Although they are highly effective in cell culture and in animal models, they have not been applied to the treatment of human conditions. Some groups have developed recombinant adenovirus (AV), adeno-associated virus (AAV) or herpes simplex virus type 1 (HSV) vectors that were used for local delivery and expression of neurotrophic factors in dorsal root ganglion neurons, which protected against the development of neuropathy in animal models without causing systemic side effects [20, 27, 31]. In other studies, HSV vectors expressing pro-enkephalin were shown to mediate the release of opioid peptides from afferent nerve terminals in the spinal cord and to result in localized antinociceptive effect in animal models of pain [7, 11, 12, 26–28]. Targeted gene delivery using recombinant virus vectors offers an excellent means to utilize short-lived peptides to produce specific effects in spatially limited compartments of the CNS. Wilson *et al.* (1999) engineered an HSV vector to express the cDNA for an opioid peptide precursor, human preproenkephalin, under the transcription control of the cytomegalovirus promoter [28]. When inoculated subcutaneously in mice, presence of virus in neuronal cells in spinal ganglia and of human proenkephalin in the central terminals of these neurons indicated appropriate transgene delivery and expression. In animals treated with preproenkephalin-HSV, hyperalgesia was selectively blocked without disrupting baseline sensory neurotransmission. This blockade of sensitization was reversed by administration of the opioid antagonist naloxone. The results of this proof-of-principle study demonstrated that the function of spinal sensory neurons can be selectively altered by virus-mediated delivery of an opioid precursor-encoding transgene [28]. The used hyperalgesic animal model has some relevance to establishing and maintaining chronic neuropathic pain in humans, and this approach may be therefore useful as a clinical treatment of chronic pain and hyperalgesia. In a more recent study, Hao *et al.* (2003) confirmed that HSV vector-mediated expression of proenkephalin in a rodent model of neuropathic pain is able to produce antiallodynic effects that are reversed by naloxone [12]. In addition, these authors found that the effect of HSV-mediated proenkephalin expression enhances the effect of simultaneously administered morphine. In a separate study, Hao *et al.* (2003) administered an HSV vector expressing glial cell-derived neurotrophic factor (GDNF) in a similar rodent model of neuropathic pain [13]. Subcutaneous injection of the vector one week after sciatic nerve ligation resulted in a significant antiallodynic effect that was maintained for 3–4 weeks. Reinoculation of the vector established the same antiallodynic effect with a magnitude at least equivalent to the initial effect [13].

Instead of gene transfer to the neural and glial cells, Finegold *et al.* (1999) have transferred genes to the meninges surrounding the spinal cord and used transduced meningeal cells as biological pumps releasing active peptide [7]. These authors used a recombinant AV vector carrying the cDNA for a secreted form of the endogenous opioid beta-endorphin. In an inflammation model of chronic pain, administration of the AV vector to the CSF transduced meningeal cells and the resulting increase in beta-endorphin secretion attenuated inflammatory hyperalgesia, yet had no effect on basal nociceptive responses [7]. Liu *et al.* (2004) constructed a replication-incompetent HSV vector encoding the human glutamic acid decarboxylase (GAD67) gene [14]. Dorsal root ganglion neurons transduced by this vector in culture or *in vivo* produced GAD and released GABA constitutively. Subcutaneous inoculation of the AV vector in the lower extremities in an animal model of central neuropathic pain reduced both mechanical allodynia and thermal hyperalgesia. Vector-mediated GABA release attenuated

the increase in spinal calcitonin gene-related peptide immunoreactivity caused by cord hemisection [14].

Targeted toxins

A number of targeted toxins have already been used in animal pain research. These include axonally transported agents such as the immunotoxin OX7-saporin, or neuropeptide-toxin conjugates such as substance P-saporin. These and other related agents produce controlled neuronal death by selectively delivering ribosome inactivating proteins (RIP) to specific types of neurons. The effector toxin moiety of choice is the RIP, saporin, a 30-kDa plant endoglycosidase [24, 25].

The most promising targeted toxins seem to be recently developed agents consisting of saporin coupled to a neuropeptide. Substance P-saporin seems currently the most widely used neuropeptide-toxin conjugate [25]. Its remarkable effects on nociception in animal models suggests this agent may be clinically useful. More agents based on monoclonal anti-neuronal antibodies or ligands are being tested in preclinical trials and some of them may be therapeutically useful in humans [24].

Botulinum neurotoxins are another class of naturally occurring targeted toxins. They work by inhibiting the release of acetylcholine from peripheral cholinergic nerve terminals. More recently, additional effects on non-cholinergic pathways have been identified. Foster (2004) reviewed the potential use of different serotypes of botulinum toxin for treatment of pain [9]. Botulinum neurotoxins have been demonstrated to benefit a range of chronic pain syndromes. A novel hybrid protein derived from botulinum neurotoxin type A, LH(N)/A-ECL, has been demonstrated to selectively target nociceptive afferent neurons and inhibit the release of neurotransmitters involved in pain transmission. This novel derivative of botulinum neurotoxin type A develops prolonged analgesic activity *in vivo*. Mense (2004) speculated on another site of analgesic action of botulinum neurotoxins, postganglionic sympathetic nerve endings that use the pronociceptive substances norepinephrine and ATP as transmitters [16]. Botulinum toxins may inhibit the release of these transmitters and exert analgesic effects in cases of sympathetically maintained pain including the complex regional pain syndrome.

Antisense nucleotides

Antisense oligonucleotides were recently introduced to the functional characterization of individual proteins that cannot be specifically targeted using pharmacological agents, and seem to provide a very useful tool for determining the mechanism of action of these pharmacological agents. As a functional genomics tool for target identification and validation, antisense technology offers a screening method for potential new therapies and its use can streamline and accelerate the process of drug discovery [22]. Finally, antisense oligonucleotides have the potential to serve as therapeutic agents in humans. Antisense inhibition of gene expression relies upon nucleic acid base pairing. Antisense oligonucleotides, typically 15–25 nucleotides in length, are designed to bind to a complementary sequence on the target RNA. As a consequence, the protein product coded by that particular RNA is not synthesized [22]. A variety of pain-relevant proteins have been targeted with antisense oligonucleotides. Many of these studies have made significant contributions to our understanding of the neural mechanisms of pain and analgesia. Targets of such studies were ion channels (e.g. P2X receptors), voltage-gated sodium channels, G-proteins and G-protein coupled receptors, opioid receptors, α-adrenergic receptors, glutamate receptors, and other signaling molecules and growth and transcription factors [22]. In the relatively short period of time since their introduction, antisense oligonucleotides have contributed greatly to the field of pain and analgesia. Nevertheless, antisense oligonucleotide-based approaches have failed to meet the high expectations initially placed upon them. This failure can be largely attributed to an underestimation of the complexity of antisense technology and a lack of appropriate tools for its successful administration [10, 17, 22]. Antisense oligonucleotides for therapy of chronic pain are still far away from clinical studies and currently remain at the stage of initial preclinical trials in animal models [22].

Summary and conclusions

Chronic pain is a frequently underestimated medical condition which represents a complex therapeutic challenge. Currently used analgesic drugs often fail to provide satisfactory pain relief and may cause serious side effects if overdosed. Local administration of naturally occurring or recombinant molecules, virus-mediated transfer of peptide/protein encoding transgenes, and cell-mediated release of analgesic substances are recently developed and rapidly evolving methods for spatially limited modulation of pathological nociception within defined compartments of the CNS. Most strate-

gies in preclinical and clinical studies involve agents targeting the spinal cord, an important structure for the generation and processing of nociceptive signals.

There seems to be a great potential of these targeted biological therapies for improvement of standard analgesic drugs and for validation of new molecular targets involved in nociception. There is also no doubt that recent progress with recombinant molecules and with virus and cell vectors has allowed significant advancement of the experimental therapies for pain. However, despite numerous exciting and promising preclinical studies in animal models of chronic pain, clinicians may be more than a decade away from advanced clinical trials utilizing the strategies explored in these studies.

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