Nerve Tubes for Peripheral Nerve Repair

Godard C.W. de Ruiter, MD[a], Robert J. Spinner, MD[b,c], Michael J. Yaszemski, MD, PhD[c], Anthony J. Windebank, MD[d], Martijn J.A. Malessy, MD, PhD[a,*]

KEYWORDS

• Nerve tubes • Nerve guides • Nerve conduits
• Animal models • Evaluation methods
• Clinical nerve repair • Modified nerve tubes

At this moment, the gold standard for repair of nerve defects that cannot be directly restored without tension to the nerve ends is still the autologous nerve graft (**Fig. 1**A). Most commonly, the sural nerve is used, taken from the leg of the patient. Obviously, repair with autografts has several disadvantages, such as the need for an extra incision, limited availability, mismatch in size of the damaged nerve and the donor nerve, and the chance for the development of a painful neuroma. Because of these disadvantages, various alternatives have been developed for autograft repair (eg, repair with autogenous venous grafts[1] and nerve allografts,[2,3] and nerve tubes, guides, or conduits). Practical advantages of nerve tubes are the unlimited right-off-the-shelf availability in different sizes that match the damaged nerve (**Fig. 1**B). Besides, functional recovery is often reduced after autograft repair compared with direct coaptation repair. A possible explanation is that axons need to cross two coaptation sites, which might decrease the number of axons reaching the distal targets and lead to increased misdirection of regenerating axons.[4] An ideal alternative, therefore, will also lead to improved regeneration and functional results of nerve repair. In this article, the authors give an overview of the current experimental and clinical data on nerve tubes for peripheral nerve repair. The goal of this article is not to be complete but to provide an overview of the nerve tube literature and to analyze critically the data on which the step from laboratory to clinical use is based.

DEVELOPMENT OF NERVE TUBES

The Concept of Nerve Tube Repair

The first attempts at nerve tube, entubulation, or tubulization repair date back to the end of the nineteenth century (see Table 1 in the article by Weiss elsewhere in this issue).[5] The results of these first attempts were disappointing and later viewed by Sunderland[6] as only of historical interest. The concept of the nerve tube was reintroduced in the 1980s, mainly as a tool to investigate the process of regeneration. In the beginning, silicone tubes were used mostly. Later, nerve tubes of other synthetic nonbiodegradable[7–11] and biodegradable materials (including polymers of glycolic and lactic acid,[12–14] and caprolactone[15,16]) were developed. These first experiments with silicone nerve tubes by Lundborg and colleagues[17] demonstrated that axons can successfully regenerate across a 1-cm gap in the rat sciatic nerve model. No regeneration was observed in the absence of the distal nerve stump and across 15-mm defects, which was later explained by the accumulation of neurotrophic factors in the silicone chamber that

[a] Department of Neurosurgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA
[c] Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA
[d] Department of Neurology, Mayo Clinic, Rochester, MN, USA
* Corresponding author.
E-mail address: M.J.A.Malessy@lumc.nl (M.J.A. Malessy).

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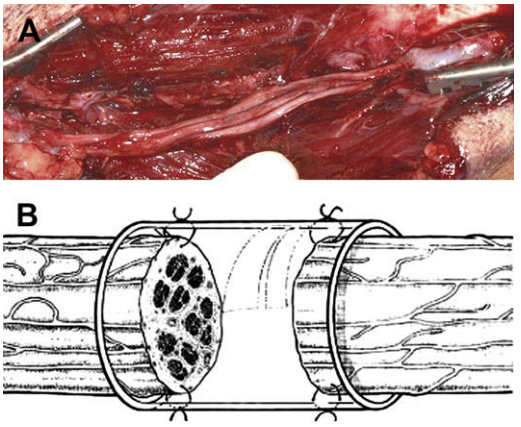

Fig. 1. (*A*) Repair of a radial nerve lesion (after a humerus fracture) with autologous sural nerve grafts. (*B*) Nerve tube repair. (*Adapted from* Lundborg G, Dahlin LB, Danielsen N. Ulnar nerve repair by the silicone chamber technique: case report. Scand J Plast Reconstr Hand Surg 1991;25:79–82; with permission.)

probably only act over a limited distance (neurotropism or chemotaxis). Another explanation might be that the formation of a fibrin matrix (**Fig. 2**), which is essential in the process of regeneration,[18] does not occur if the gap is too long.[19]

Physical Characteristics of the Nerve Tube

Other physical properties, including the dimensions of the nerve tube, prefilling with phosphate-buffered saline (PBS),[20] and porosity,[19] have also been shown to affect the formation of the fibrin matrix. Jenq and Coggeshall[21,22] found that the addition of holes to silicone nerve tubes increased the number of myelinated axons and the length of the gap that could be bridged. Possible explanations were that by adding holes, cells (eg, macrophages and leucocytes) and molecules (eg, fibrin and fibronectin) involved in the formation of the fibrin matrix could enter the site of regeneration. The importance of the permeability of the nerve tube was later confirmed in other experiments,[15,23–26] although what the ideal pore size is exactly (microporous or macroporous) still remains questionable. Disadvantages of macropores might be that neurotrophic factors can diffuse out of the nerve tube and that the fibrin matrix might be disorganized (orientation perpendicular to the pores instead of longitudinal). Permeability not only depends on pore size but may also be affected by, for example, hydrophilic properties of the material. Next to permeability, the surface texture and dimensions of the nerve tube have been found to affect the formation of the fibrin matrix;[8] with smooth surfaces (eg, in silicone nerve tubes), the longitudinal matrix coalesces and forms a free-floating nerve cable, whereas with rough surfaces, the tissue disperses and completely fills the lumen of the nerve tube.[27]

With the potential use of nerve tubes, especially biodegradable nerve tubes, for clinical nerve repair, other physical characteristics were also investigated, including swelling and degradation properties. Swelling of a nerve tube might primarily block the lumen for regeneration or might secondarily lead to compression of the regenerated nerve. Degradation may cause swelling owing to the accumulation of degradation products that can increase the osmotic pressure in the tube.[16,28] Besides, degradation products might be toxic or might interfere with the process of regeneration. Degradation may also, in time, affect the porosity and tensile properties of the nerve tube. These tensile properties are important because a nerve tube should be flexible for implantation into mobile limbs but at the same time, the nerve tube should be resistant to deformation (elongation, breaking, or kinking) and strong enough to hold a suture. Transparency is preferred for suturing and accurate positioning of the nerve stumps. In the end, nerve tubes must be sterilizable without compromising the physical properties mentioned above. **Table 1** summarizes the known physical properties of some of the frequently used nerve tubes. It is important to note the physical properties of the nerve tube depend not only on the biomaterial but also on other factors, such as the dimensions of the nerve tube and fabrication technique. Not all nerve tubes that are currently available for clinical use have been characterized extensively in vitro before clinical application.

Evaluation Methods and Animal Models

Different evaluation methods and animal models have been used to investigate the process of regeneration across nerve tubes. Most experiments have been performed in the rat sciatic nerve model. Commonly used evaluation methods in this model include electrophysiology, nerve morphometry, and walking track analysis (see **Table 1**). The first, most important observation, however, is the percentage of successful regeneration across the nerve tube. Failures due to collapse, swelling, and suture pullout have been reported.[12,14,29,30] The second most important observation is the quantity of regeneration across the nerve tube. This quantity is mostly determined for the number of axons (myelinated or unmyelinated) at the middle part or distal to the nerve tube and is then preferably compared with the numbers in normal nerve and after autograft repair. However, the numbers

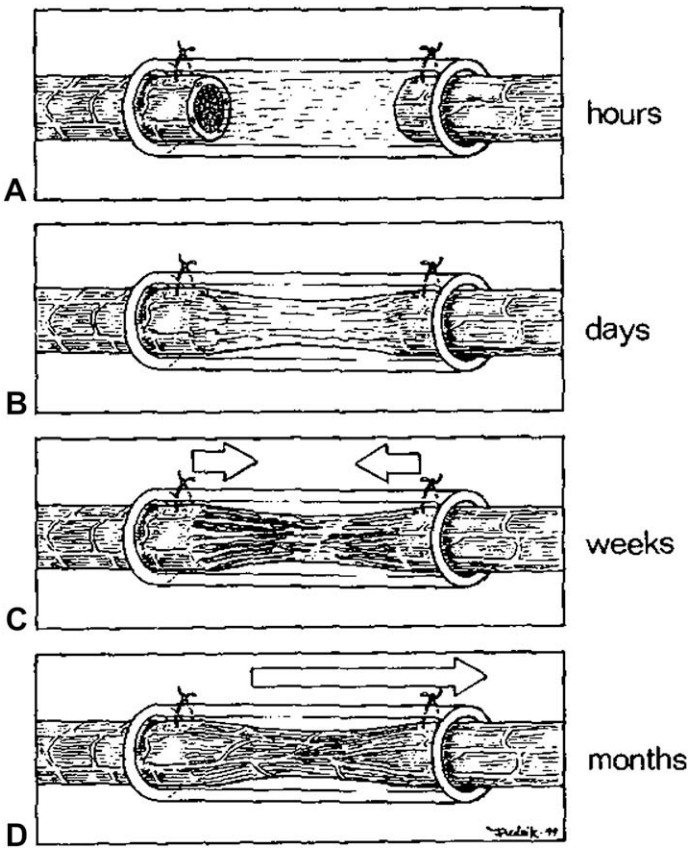

Fig. 2. The different phases in the process of regeneration across the nerve tube. (*A*) Within hours of implantation, the lumen fills with fluid containing neurotrophic factors and various inflammatory cells. (*B*) Within days, a fibrin matrix is formed between the nerve stumps. (*C*) In weeks, Schwann cells, fibroblasts, and microvessels migrate along the fibrin matrix from both proximal and distal nerve ends. (*D*) In months, axons regenerate from the proximal nerve stump into the matrix. (*From* Dahlin L, Lundborg G. Use of tubes in peripheral nerve repair. Neurosurg Clin N Am 2000;12(2):341–52; with permission.)

of axons that have been reported in the literature differ.[31] Sometimes only the density of nerve fibers in a specified area is provided (see **Table 1**).[32,33] This area may not be representative of the total cross-sectional area of the nerve. Also, the total number of axons may not be the best parameter to quantify regeneration, because this number is increased early in the process of regeneration because of collateral sprouting or branching, and has been found to decrease later.[34] Different factors may stimulate the sprouting or branching of axons (eg, the addition of Schwann cells[35–37] or neurotrophic factors). Numbers may increase without an actual increase in the number of motoneurons and dorsal root ganglion cells from which axons have regenerated across the nerve tube. In the authors' opinion, quantification of regeneration across the nerve tube can therefore best be performed with retrograde tracing. The technique with fluorescent dyes that are retrogradely transported to the motoneuron or dorsal root ganglion can also be used to analyze the accuracy of regeneration across the nerve tube. For example, different tracers can be applied sequentially to the same nerve branch before and after nerve repair to determine the direction of regenerating axons, or simultaneously to different nerve branches (eg, the tibial and peroneal nerves) to determine the dispersion of regenerating axons across the nerve tube.[38] Although it has often been suggested that nerve tube repair leads to an improved orientation of regenerating nerve fibers, only a few studies have actually investigated the accuracy of regeneration across the nerve tube.[39–43] These studies did not show an improved accuracy after nerve tube repair compared with direct coaptation or autograft repair. Brushart and colleagues[44] actually found that regenerating axons might disperse across the tube and that this dispersion increases with gap length. This dispersion of regenerating axons might lead to (1) misdirection of regenerating axons or (2) polyinnervation of different targets by axons originating from the same neuron. In comparison, autograft

Table 1
Experimental data on some of the frequently used nerve tubes

Nerve Tube					Model			Evaluation		
Material	Permeability	Flexibility[a]	Degradation	Swelling	Animal	Nerve	Gap Size	Methods	Control	Follow-Up
Natural										
Collagen[53,54,116]	Diffusion of molecules up to 215 Å	—	—	3 × dry weight	Monkeys Rats	Median Sciatic	4, 5 mm 4 mm	Number of axons, electrophysiology Electrophysiology	Reversed autograft and normal, direct coaptation, and negative controls	Up to 760 d 4 and 12 wk
Synthetic										
Nonbiodegradable										
Silicone[17]	—	—	—	—	Rat	Sciatic	6, 10, 15, 20 mm	Nerve histology	Absence distal nerve stump	1 mo
Hydrogel, p(HEMA-co-MMA) 86:14[b,29,117]	[c]	[c]	—	—	Rat	Sciatic	10 mm	Percentages successful regeneration, nerve morphometry	Isografts	8 and 16 wk
Biodegradable										
PGA[33]	—	—	—	—	Monkeys	Ulnar	3 cm	Electrophysiology, nerve fiber density	Sural nerve grafts	1 y
PLA[118]	83.5%, 12.1 μm[d]	80 MPa 1.0 MPa	Mn 43% at 8 wk	—	Rats	Sciatic	1 cm	SFI, gastrocnemius muscle weight, nerve fiber density	Reversed isograft	16 wk
PLGA,[119] 75:25	83%, 20 μm[d]	8 MPa 0.95 MPa	Mn 38% at 8 wk	—	—	—	—	—	—	—

PLC,[15,120] 50:50	Low and high[e]	3 MPa 25 MPa	Mn 50% at 10 mo	—	Mice	Sciatic	6 mm	Percentages successful reinnervation, number of axons, electrophysiology, sweating tests	Silicone, Teflon, collagen, polysulfone	4, 5 mo
					Rats	Sciatic	8 mm	Simultaneous retrograde tracing, electrophysiology, SFI	Normal, autograft, silicone	90 d
PLC,[32,121,122] 50:50 (DL 85:15)		2.5 MPa[f]	45% mass loss at 8 mo	300% volume increase at 3 mo	Rats	Sciatic	1 cm[32] 15 mm[122]	Nerve fiber density Electrophysiology, video analysis	Reversed autograft	10 wk 5 mo
TMC-CL,[123] 50:50	No pores[g]	23.5 MPa 1 MPa	—	—	—	—	—	—	—	—

Abbreviations: DL, L (left) and D (Dexter) lactides; HEMA-co-MMA, hydroxyethyl methacrylate-co-methyl methacrylate Mn, average molecular weight; MPa, megapascal; PGA, polyglycolic acid; PLA, poly(L-lactic acid); PLC, poly(DL-lactide-ε-caprolactone); PLGA, poly (DL-lactic co-glycolic acid); SFI, sciatic function index; TMC-CL, trimethylene carbonate-co-ε-caprolactone.

[a] Elastic modulus, tensile strength.

[b] Poly(2-hydroxyethyl methacrylate-co-methyl methacrylate).

[c] Depending on ratio HEMA:MMA, microporous and macroporous determined with surface electron microscopy.

[d] Porosity and mean pore size, measured by mercury porosimetry.[119]

[e] Low prepared with fine powder of amylose (<10 μm), high with glucose of around 10 μm; permeability tested with ultraviolet spectroscopy.

[f] Rapid loss after 3 weeks.[121]

[g] But slow diffusion of methylene blue molecules, analyzed with ultraviolet spectroscopy.

repair contains more regenerating branched axons to the inside of the basal lamina tubes.[45]

Functional analysis is ultimately the most important method for translating the results of nerve tube repair into patients. This type of analysis has not often been included in the evaluation of nerve tube repair. The reason might be that the most commonly used method, the sciatic function index (SFI), is based on footprint analysis[46,47] and lacks sensitivity, which might be because of contractures[48] and autotomy[49] but also because the SFI evaluates the distal foot muscles that often do not recover because of the prolonged time of denervation.[50] The authors, therefore, recently introduced the use of two-dimensional motion analysis to measure the recovery of more proximally located muscles from the ankle angles of maximum plantar and dorsiflexion during the stance and swing phases.[51] This method was found to be more sensitive than the SFI and is currently being used by their laboratory for functional analysis after different nerve repair techniques. Another advantage of functional analysis in comparison with other evaluation methods is that animals can be evaluated at multiple time points. Combined with electrophysiology, this method can provide insight into the time to reinnervation and recovery.

Electrophysiology is frequently included in the evaluation of results after nerve tube repair. Most often, compound muscle action potentials (CMAPs) are recorded and analyzed for amplitude, area under the curve, or latency.[31] This method is not as time consuming as most other evaluation methods, but it should not be used instead of functional evaluation. CMAP recovery after nerve repair may be better than functional recovery because of distal sprouting, which results in larger motor units, and because of misdirected axons that contribute to the CMAP but probably not to recovery of function.[54]

Different animal models have also been used for the analysis of nerve tube repair, including mice, rabbits, and monkeys (see **Table 1**). The disadvantage of this use of larger animal models is that it makes it difficult to compare the results between studies, especially the extrapolation of the size of the nerve gap.[52] An obvious advantage of larger animals is the closer-to-human comparison, especially for the primate model. The polyglycolic acid (PGA) and collagen nerve tube (which are now available for clinical use, see later discussion) were first investigated experimentally in monkeys.[33,53,54] In 1988, Dellon and Mackinnon[33] published the first study in which they compared repair of a 3-cm gap in the ulnar nerve (proximal to the elbow) in adult male *Macaca cynomolgus* monkeys with sural nerve grafts and solid and mesh PGA tubes (eight repairs per group). After 1 year of follow-up, nerve fiber densities did not differ from normal after the different repair techniques. Unfortunately, absolute numbers of nerve fibers were not provided. Electromyography demonstrated recovery in 19 out of 28 (68%) of the intrinsic muscles studied in the solid and mesh tube groups (2 muscles per repair, seven repairs per group). Recovery after autograft repair was not reported because the Martin-Gruber anastomosis in this group had not been divided. Electromyography results were reported for 7 tube repairs, because one case of solid tube repair had no continuity (the reason for exclusion of one of the mesh tubes was not reported). In three out of seven solid and four out of eight mesh tubes, some scar tissue was observed in the center of the tube. Later, the same investigators published another study performed in monkeys, in which regeneration across 2- and 5-cm nerve gaps in radial sensory and ulnar nerves was compared for crimped and mesh glycolide trimethylene carbonate (Maxon) and collagen nerve tubes.[55] Poor regeneration was found in that study[55] across 5-cm nerve gaps.

Archibald and colleagues[53] compared repair of 4-mm gaps with collagen nerve tubes and autografts (reversed segments) in rats (sciatic nerve) and *Macaca fascicularis* monkeys (median nerve, 2 cm above the wrist). This study showed that collagen nerve tube repair was as effective as autograft repair in terms of physiologic responses from target muscle and sensory nerves. Later, they reported a second study on collagen nerve tube repair of 5-mm gap median nerve lesions (again, 2 cm above the wrist) in monkeys, which included 3 years of electrophysiologic assessment and nerve morphometry.[54] In this study, a significantly increased number of axons distal to the repair site (1.2 to 2 times larger) was found after both collagen nerve tube and autograft repair.

CLINICAL USE OF NERVE TUBES FOR PERIPHERAL NERVE REPAIR

Currently, various nerve tubes are available for clinical nerve repair: Neurotube (PGA), Neuragen (collagen), Neurolac (polycaprolactone), NeuroMatrix and Neuroflex (both collagen), and SaluBridge (hydrogel, nonbiodegradable).[56] These nerve tubes are mainly used in the repair of small nerve gaps (<3 cm) in small sensory nerves, such as digital nerve lesions. In addition, recently a processed allograft (Avance) has become available for clinical use. In this article, the authors only discuss the results of the large series and randomized studies

that have been reported on the clinical use of the silicone, PGA, and poly(DL-lactide-ε-caprolactone) (PLC) nerve tubes. In addition, series have been reported on the use of nonbiodegradable polytetrafluoroethylene (PTFE) nerve tubes (GORE-TEX or Teflon) for median and ulnar nerve[57] and inferior alveolar/lingual nerve lesions,[58,59] a small series on the use of collagen (Neuragen) nerve tubes in the repair of obstetric brachial plexus injuries,[60] and several cases on the use of PGA nerve tubes (for the repair of the inferior alveolar nerve,[61] medial plantar nerve,[62] zygomatic and buccinatory branches of the facial nerve,[63] and spinal accessory nerve;[64] for nerve reconstruction after a hallux-to-thumb transfer;[65] and for interfascicular median nerve repair with multiple PGA tubes).[66] Combinations of PGA tubes with collagen sponges[67,68] and an interposed nerve segment[69] have also been used in patients, and a chitosan tube with internal oriented filaments of PGA[70] (see section on modifications to the common hollow nerve tube).

Silicone Nerve Tubes

In 1997, Lundborg and colleagues[71] published their first results of 1-year follow-up of a prospective randomized study, in which small defects (3–4 mm) after fresh and complete clean-cut transection of the ulnar and median nerves proximal to the wrist (up to 10 cm) were repaired with silicone nerve tubes (11 patients) or conventional microsurgical direct coaptation repair (8 patients). Several tests were used to evaluate the results (see **Table 2**). In general, no significant differences were found between the two types of repair. Also in the 5-year follow-up (2004),[72] no significant difference in outcome was found, except for significantly less cold intolerance after silicone nerve tube repair. The use of silicone nerve tubes, however, has been heavily criticized,[73,74] mainly because of the potential late compression of the nerve by the nonbiodegradable tube. Critics often refer to a study by Merle and colleagues,[75] in which silicone tube (1 patient) and sheath repair (2 patients) resulted in chronic nerve compression. In addition, a study by Braga-Silva[76] was reported on silicone nerve tube repair of median and ulnar nerve lesions (up to 3 cm) in which 7 out of 26 patients requested removal of the nerve tube because of local discomfort. Dahlin and Lundborg[77] themselves performed a re-exploration surgery in 7 patients, as an ethically permitted part of their prospective study (4 patients complained of local discomfort), but found no signs of neuroma and only a mild microscopic foreign body reaction in 2 cases. After removal of the silicone nerve tube, no new impairment of nerve function occurred. They emphasized that in their studies, silicone nerve tubes were used with a diameter exceeding the diameter of the nerve by at least 30%. Nevertheless, they acknowledged that a biodegradable nerve tube would be better, provided that it degrades with minimal tissue reaction and without impairment of nerve regeneration.[78]

Polyglycolic Acid Nerve Tubes

In 2000, Weber and colleagues[79] presented the results of the first multicenter randomized study on the repair of digital nerves with gaps up to 3 cm using glycolic acid (PGA) nerve tubes. Ten years before that, Mackinnon and Dellon[80] had already presented a series of 15 patients in which they had also used PGA nerve tubes to repair digital nerve defects up to 3 cm. In that study, excellent results were reported for 5 patients (33%), good results for 8 patients (53%), and poor results for 2 patients (14%). In the randomized study by Weber and colleagues,[79] PGA nerve tube repair was compared with standard repair (direct coaptation for gaps less than 8 mm and nerve graft repair for gaps greater than 8 mm). The overall results at 1-year follow-up showed no significant difference between the two groups, with excellent and good outcome in respectively 44% and 30% of the repairs with PGA nerve tubes compared with 43% of both excellent and good outcome after standard repairs. The investigators subsequently performed a subgroup analysis for different gap lengths ($\leq$4 mm, 5–7 mm, and 8 mm–3 cm) that demonstrated excellent results for gaps less than or equal to 4 mm for moving two-point discrimination (m2PD) in 91% of PGA nerve tube repairs compared with 49% of standard repairs (P = .02). As noted by Lundborg in the discussion on this article, the statistics of this study are difficult to interpret because of the heterogeneous data (eg, different levels of injury and mechanisms of injury were included). Also, the numbers per group of PGA nerve tube and standard repair for subgroup analysis were not provided. However, it is not clear why separate subgroup analysis was performed for gaps less than or equal to 4 mm. Although the investigators mention that it is generally accepted that 4 mm is the maximum gap length for digital nerves to be repaired with minimal tension by the end-to-end method, in the standard repair group all gaps of 5 to 7 mm were repaired by direct coaptation. In the 5- to 7-mm gap group, excellent results were obtained in only 17% of the PGA nerve tube repairs and 57% of the standard repairs (P = .06). The technique used to measure two-point discrimination was not based on the Moberg

Table 2
Clinical data on the use of nerve tubes in large series and randomized controlled clinical trials

Nerve Tube							Evaluation			
Material	First Author (y)	Study Type	Numbers	Patient Age (y)	Nerves, Location	Gap Size	Methods	Control	Interval	Follow-Up Period
Synthetic										
Nonbiodegradable										
Silicone	Lundborg (1997)[71]	RCT	11 patients, 8 controls	12–72, mean 29	Median and ulnar, <10 cm proximal to wrist	3–4 mm	Tactilometry, s2PD,m2PD, and strength abduction dig its I and II[a]	Direct repair	No	1 y
	Lundborg (2004)[72]	RCT	17 patients, 13 controls	12–72, mean 32		3–5 mm	Model instrument for outcome after nerve repair,[124] neurophysiology			5 y
Biodegradable										
Polyglycolic acid	Mackinnon (1990)[80]	Series	15 patients, 16 repairs	30.5 (SD 7.6)	Digital	0.5–3.0 cm, mean 1.7	s2PD and m2PD: Excellent[c]: ≤6 mm and ≤3 mm	No Gap <8 mm direct repair;	None placed acutely	11–32 mo, mean 22.4
	Weber (2000)[79]	RCMT	62 repairs, 74 controls	17–65, mean 35	Digital, distal to wrist	7.0 mm,[b] control 4.3	Good: 7–15 mm and 4–7 mm Poor: ≥15 mm and ≥7 mm	Gap >8 mm nerve graft	50 < 72 h; 54–20 d; 7 > 20 d	Mean 9.4 mo, Control 8.1
	Battiston (2005)[82]	Series	19	15–67, mean 40	Digital	1.0–4.0 cm, mean 2.0	s2PD and m2PD, MRC, quick-DASH	Muscle–vein combined conduits	Primary: 16 mo	6–74 mo, mean 30
PLC	Bertleff (2005)[83]	RCMT	21, 13 controls	Mean 43	Digital, distal to wrist	Up to 2.0 cm	s2PD and m2PD	Direct repair	Not provided	1 y

Abbreviations: m2PD; moving two-point discrimination; MRC, strength for British Medical Research Council scale; PLC, poly(DL-lactide-ε-caprolactone); quick-DASH, disabilities of the arm, shoulder, and hand; RCMT, randomized controlled multicenter trial; RCT, randomized controlled clinical trial; s2PD, static two-point discrimination; SD, standard deviation.

[a] Tactilometry for perception of vibration was measured with Semmes-Weinstein monofilaments, s2PD and m2PD were measured using Moberg's method,[81] and the strength of abduction digits I and II was measured with an intrinsicmeter. In addition, the presence of a neuroma, hyperesthesia, and cold intolerance were noted.

[b] A gap of 5 mm was left intentionally, even in defects of 0 to 4 mm.

[c] In Weber study, outcome was defined for the lower of the s2PD or m2PD, as defined in the study by Mackinnon and Dellon, except that excellent outcome was defined for m2PD less than or equal to 4 mm.

approach,[81] with application of light pressure (just enough to blanch the skin), but with increasing pressure until the stimulus was perceived by the patient (see discussion by Lundborg).

Another large series on PGA nerve tube repairs of 19 digital nerves in 17 patients who had gaps up to 4 cm was published in 2005 by Battiston and colleagues.[82] In this study, very good results (S3+ and S4, defined for static two-point discrimination [s2PD] up to 15 mm) were reported for 13 patients (76.5%) and good results in 3 patients (17.7%). Analysis of the data, however, shows that in only 2 patients, S4 (s2PD 2–6 mm) was obtained and that no results were excellent for m2PD ($\leq$3 mm, by the definition used in the studies by Mackinnon[80] and Weber;[79] see **Table 2**), and good results were obtained (m2PD 4–7 mm) in only 4 out of 19 repairs.

In conclusion, PGA nerve tubes might lead to results comparable to conventional nerve repair in the repair of small gaps in digital nerve lesions, but care should be taken with the interpretation of the data and the wide application to the repair of other nerve lesions based on these results.

Poly(DL-Lactide-ε-Caprolactone) Nerve Tubes

In 2003, Bertleff and colleagues[83] presented the results of a multicenter trial on digital nerve repair for gaps up to 2 cm that compared PLC nerve tube and standard repair, which were all direct coaptation repairs (with the finger flexed to reduce tension). Randomization was performed separately for gaps less than or equal to 4 mm, 4 to 8 mm, and 8 to 20 mm. Sensory recovery was evaluated at 3, 6, 9, and 12 months for the s2PD and m2PD measured with the pressure-specified sensory device.[84] Two-point discrimination for PLC and direct coaptation repair of gaps up to 2 cm showed no significant differences, but unfortunately, results for subgroup analysis were not provided. The pressure that was applied (to feel the stimulus) seemed larger in the PLC nerve tube repair group than in the direct repair group.[83] More wound healing problems were observed after PLC nerve tube repair than after direct coaptation. In a recent review, Meek and colleagues[85] also commented that small fragments of biomaterial in experiments with PLC nerve tubes were still found 24 months after implantation and that PLC nerve tubes are normally stiff and only flexible after putting in warm saline before implantation. A more extensive report on the use of PLC nerve tubes (according to the investigators) will soon be published.[85] So far, ample evidence supports the clinical use of PLC tubes.

Conclusion: Clinical Use Nerve Tubes

In conclusion, in the authors' opinion at this moment, care should be taken with the wide use of tubes in peripheral nerve repair, not only because of the concerns mentioned above but also because of the following reasons. First, little is still known about the accuracy of regeneration across nerve tubes. In the repair of larger mixed or motor nerves, dispersion of regenerating axons across the nerve tube may lead to misdirection and polyinnervation (see section on the development of nerve tubes) and result in impaired functional recovery because of, for example, cocontraction or synkinesis. In most experimental studies on nerve tube repair, accuracy of regeneration and functional analysis were not included. Finally, not all nerve tubes that are now available for clinical use have been characterized extensively in vitro and the long-term effects of biodegradable nerve tubes have not (yet) been reported (see **Table 2**, follow-up studies 1–2 years).

MODIFICATIONS TO THE HOLLOW NERVE TUBE

Different modifications to the common hollow or single lumen nerve tube have been investigated to enhance regeneration and extend the gap that can be bridged (**Fig. 3**). Prefilling of the nerve tubes with PBS and the addition of pores have already been mentioned in the section on the development of nerve tubes. In the following section, the authors briefly discuss the addition of different extracellular molecules (collagen and laminin), internal frameworks, supportive cells, and nerve growth factors.

Collagen and Laminin-Containing Gels

Collagen and laminin are involved in the process of regeneration by forming a substrate for the migration of nonneuronal cells. Filling of silicone nerve tubes with collagen and laminin-containing gels has been shown to increase the rate of regeneration[11] and the gap that can be bridged (up to 15–20 mm).[86] This effect, however, depends on several factors, including the concentration[87] and the permeability of the nerve tube.[88] Alignment of the collagen (gravitational or magnetic) may also further enhance regeneration.[89] Currently, different collagen and laminin-containing gels (eg, BD Matrigel) are being used for the incorporation of supportive cells and growth factors.[37,90,91] Also, oligopeptides derived from laminin-integrin active sites are being investigated for a potential role in the guidance of regenerating axons.[92]

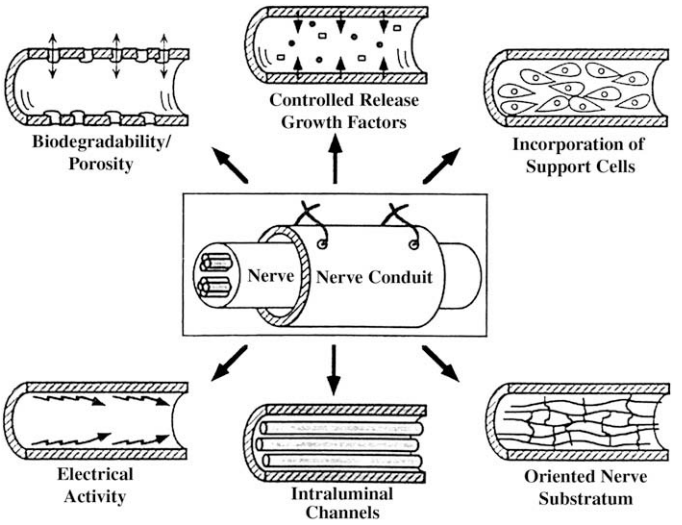

Fig. 3. Different modifications to the single lumen nerve tube or conduit. (*From* Hudson TW, Evans GR, Schmidt CE. Engineering strategies for peripheral nerve repair. Clin Plast Surg 1999;26:617–28; with permission.)

Internal Framework

An intrinsic framework may also enhance regeneration and increase the gap that can be bridged because of stabilization of the fibrin matrix that is formed inside the nerve tube. Different internal structures have been investigated, including polyamide filaments,[93] laminin-coated fibers,[94] PGA filaments,[95] and collagen sponges.[94,96] The combinations of PGA tube and collagen sponge, and chitosan tube and PGA filaments, have already been used clinically, although little information exists on the effect of these internal structures on the accuracy of regeneration. Different tissues have also been added to the nerve tube (eg, interposed nerve segments[97] and denatured muscle).[98] In addition, nerve tubes with a modified microarchi tecture have been developed. Yoshii and colleagues[99] developed a scaffold of longitudinally orientated collagen filaments that has been shown to lead to successful regeneration across gaps of 20 mm and even 30 mm in rats.[100] Another example of a modification to the common single lumen nerve tube structure is the multichannel nerve tube structure.[28,38,101–104] This structure has several advantages: It provides more surface area for cell attachment and controlled release of incorporated growth factors, and may reduce dispersion by containment of axonal branches, as in the autografts consisting of multiple basal lamina tubes.[39]

Supportive Cells

The addition of Schwann cells to the nerve tube has also been found to enhance regeneration in small gaps[36,37,90] and to extend the gap that can be bridged to about 2 cm,[35,91] although, remarkably, autograft repair in most studies still was found to be superior.[37,90,91,105,106] Schwann cells possibly stimulate regeneration by the production of a range of growth factors and extracellular molecules (laminin), and may play a mechanical role by forming a cable bridging the gap.[37] Schwann cells can also be genetically modified to overexpress certain growth factors. A disadvantage of the addition of Schwann cells is that it still requires the explantation of a donor nerve, to isolate autologous Schwann cells weeks before reconstruction. This disadvantage may be overcome in the future by the differentiation of, for example, bone marrow stem cells into Schwann cells.[107]

Growth Factors

The addition of different growth factors to the nerve tube, including nerve growth factor, glial cell derived neurotrophic factor, brain-derived neurotrophic factor, and fibroblast growth factor, has also been shown to enhance regeneration and increase the nerve gap that can be bridged (to 15 mm). These growth factors can be added directly to the tube (into a solution)[108] or can be released after absorption to fibronectin mats,[109,110] collagen matrices,[30] bovine serum albumin or from delivery systems such as subcutaneous minipumps[111] or microspheres that are incorporated during the fabrication process of the nerve tube.[112,113] The advantage of growth factors in comparison to Schwann cells is that no extra procedure is needed. The advantage of delivery of growth factors from microspheres is the potential for controlled release over an extended period of time without leakage from the tube.

Conductive Polymers

Finally, conductive polymers may also enhance regeneration across the nerve tube. Aebischer and colleagues[114] found significantly increased numbers of myelinated axons after repair with poled versus unpoled polyvinylidene fluoride tubes, possibly by accelerated axonal elongation on the charged surface. Schmidt and colleagues[115] found an almost twofold neurite outgrowth in vitro on conductive polypyrrole films after electric stimulation.

SUMMARY

In this article, the authors provided an overview of the experimental and clinical data currently available on the use of nerve tubes for peripheral nerve repair. At present, no sound scientific proof exists of the superiority of the empty hollow biodegradable nerve tubes that are now clinically used, as compared with direct coaptation or autograft repair. The repair of all sorts of nerve lesions may lead to unnecessary failures and, again, a discontinuation of interest in the concept of the nerve tube. The extensions of the applications, especially in the repair of larger mixed or motor nerves, should be carefully evaluated. Also, although the autologous nerve graft has several practical disadvantages, it still has several advantages, such as the presence of Schwann cells that secrete growth factors and basal lamina tubes that contain regenerating axons, besides the favorable properties of the natural strength and flexibility of the nerve, and the fact that it is immunocompatible. Eventually, different modifications to the single lumen nerve tube might lead to a nerve tube that is a better alternative than autologous nerve graft repair.

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