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Optimising Postoperative Pain Management in the Ambulatory Patient

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Abstract

Over 60% of surgery is now performed in an ambulatory setting. Despite improved analgesics and sophisticated drug delivery systems, surveys indicate that over 80% of patients experience moderate to severe pain postoperatively. Inadequate postoperative pain relief can prolong recovery, precipitate or increase the duration of hospital stay, increase healthcare costs, and reduce patient satisfaction.

Effective postoperative pain management involves a multimodal approach and the use of various drugs with different mechanisms of action. Local anaesthetics are widely administered in the ambulatory setting using techniques such as local injection, field block, regional nerve block or neuraxial block. Continuous wound infusion pumps may have great potential in an ambulatory setting. Regional anaesthesia (involving anaesthetising regional areas of the body, including single extremities, multiple extremities, the torso, and the face or jaw) allows surgery to

be performed in a specific location, usually an extremity, without the use of general anaesthesia, and potentially with little or no sedation.

Opioids remain an important component of any analgesic regimen in treating moderate to severe acute postoperative pain. However, the incorporation of non-opioids, local anaesthetics and regional techniques will enhance current postoperative analgesic regimens. The development of new modalities of treatment, such as patient controlled analgesia, and newer drugs, such as cyclo-oxygenase-2 inhibitors, provide additional choices for the practitioner.

While there are different routes of administration for analgesics (e.g. oral, parenteral, intramuscular, transmucosal, transdermal and sublingual), oral delivery of medications has remained the mainstay for postoperative pain control. The oral route is effective, the simplest to use and typically the least expensive. The intravenous route has the advantages of a rapid onset of action and easier titratibility, and so is recommended for the treatment of acute pain.

Non-pharmacological methods for the management of postoperative pain include acupuncture, electromagnetic millimetre waves, hypnosis and the use of music during surgery. However, further research of these techniques is warranted to elucidate their effectiveness in this indication.

Pain is a multifactorial experience, not just a sensation. Emotion, perception and past experience all affect an individual's response to noxious stimuli. Improved postoperative pain control through innovation and creativity may improve compliance, ease of delivery, reduce length of hospital stay and improve patient satisfaction. Patient education, early diagnosis of symptoms and aggressive treatment of pain using an integrative approach, combining pharmacotherapy as well as complementary technique, should serve us well in dealing with this complex problem.

Approximately 79 million surgical procedures are performed in the US each year.[1] It is estimated that about 60% of these are performed in an ambulatory setting.[2] Pain after surgery can adversely affect both physical and physiological functions (e.g. fear or anticipation of pain may inhibit the coughing needed to clear the airways of pulmonary secretions, or delay the resumption of normal gastrointestinal function). Inadequate relief of postoperative pain can prolong recovery, increase the duration of stay in the surgical suite or hospital and increase healthcare costs.[3] Despite improved analgesics and sophisticated drug delivery systems, surveys indicate that up to 86% of patients experience at least moderate, and sometimes severe, pain postoperatively.[4,5] In the ambulatory setting, the optimal control of pain becomes paramount as the ability of healthcare providers to interact directly with the patient after discharge diminishes. In addition, as facilities compete for patients, superior postoperative pain control may result in improved cost effectiveness, more appropriate and efficient use of resources, and ultimately improved patient satisfaction.

1. Methods of Postoperative Pain Management

Postoperative pain management can be divided into pharmacological and non-pharmacological methods. For the purposes of this review, pharmacological intervention is discussed in terms of the method and sites of delivery of the analgesics, which include local, regional, oral and systemic drug delivery. Non-pharmacological methods of pain relief are also discussed, along with suggested combinations of both modalities.

1.1 Pharmacological Methods

1.1.1 Local Anaesthesia

Local anaesthetics have been used since native South Americans discovered the numbing (and stimulating) effects of the coca plant.[6] Cocaine was first used medically in the 19th century but has since been replaced by other synthetic local anaesthetics with more favourable adverse effects profiles, e.g. lidocaine, bupivacaine, ropivacaine and levobupivacaine. Local anaesthetics work by inhibiting sodium channels in the nerve cell membrane, preventing them from depolarising. Local anaesthetics are widely administered in the ambulatory setting using techniques such as local injection, field block, regional nerve block, neuraxial block or even systemic administration.

When used as the primary method of anaesthesia, a local anaesthetic is usually injected before incision and augmented during the procedure with additional doses. When used in combination with general anaesthesia, local anaesthetics may be injected before, during or after the procedure. The duration of effect varies with the local anaesthetic chosen, although research is underway to perfect slow-release depot methods such as controlled microsphere dissolution.[7,8] This is an attempt to allow controlled release of a drug by compounding it with biodegradable polymers such as polyglycolic acid. The compound is then manufactured into injectable microspheres and placed in proximity to a target nerve.

With advances in drug delivery systems, local anaesthetics are also being incorporated with adjunctive drugs to enhance delivery. The inclusion of lidocaine with the fibrin glue used on post-tonsillectomy patients allowed them to resume oral intake in a significantly shorter time.[9] Sucralfate, a drug used to physically coat erosive gastrointestinal ulcers, has been used as an adjunct to local anaesthetics. In a study involving patients for laser-assisted uvuloplasties, postoperative use of sucralfate was found to significantly reduce analgesic requirements by physically coating the wound, thereby reducing mechanical irritation.[10]

Clonidine has been given to extend the duration of regional and neuraxial techniques by acting on α_2-adrenergic receptors on the spinal cord.[11] Hyaluronidase, an enzyme used to increase the spread of local anaesthetics, is also commonly used during ophthalmic procedures.[12] Epinephrine is used to prolong the action of local anaesthetics, although a recent study suggests that epinephrine may act independently on neuraxial receptors that may be involved in chronic pain.[13] Lidocaine has also recently been released in a transdermal patch for pain relief.[14] Many studies have focused on the efficacy of intra-articular injection, especially in the knee.[15-18] Intra-articular local anaesthetics, opioids and NSAIDs have all been studied,[19-21] with the benefits of local anaesthetics being the most widely documented.[3,22]

The use of continuous wound infusion pumps that instil continuous local anaesthetic into a wound has been explored. Results have been mixed, with the greatest benefit shown in minor to moderate surgeries.[23-25] However, a recent study has shown that bupivacaine wound infusion was as effective as patient controlled analgesia (PCA) in major colorectal surgery.[26] Continuous wound infusion may have great potential in an ambulatory setting but further studies are necessary to define its role.

1.1.2 Regional Anaesthesia

Regional anaesthesia involves anaesthetising regional areas of the body, including single extremities, multiple extremities, the torso, and the face or jaw. In the latter part of the 19th century, practitioners used cocaine for what was soon termed conduction anaesthesia.[27] Today, this phrase encompasses modern nerve blocks, sympathetic blocks and neuraxial blocks.

The use of regional blocks allows surgery to be performed in a specific location, usually an extremity, without the use of general anaesthesia, and potentially with little or no sedation. A predetermined amount of local anaesthetic with or without adjuvants (e.g. opioids, epinephrine and/or sodium bicarbonate) is deposited via injection in close proximity to a nerve or nerves supplying the surgical field. Combinations of short and long acting local

anaesthetics may be used to achieve rapid onset and long duration. Low current electrical stimulation may be used along with surface anatomy to help localise the nerve in order to increase the chances of a successful block. Sensory nerves are anaesthetised first because of their smaller size and peripheral location in the neural bundle. Motor nerves are the last to be blocked, but also the quickest to recover. Since the sensory nerves are typically slowest to recover, this technique has the potential added benefit of providing analgesia beyond the period of anaesthesia and motor weakness. In addition, these techniques may reduce the incidence of postoperative nausea and vomiting, and may allow for earlier discharge and performance of the surgical procedure in an ambulatory setting, provided the recovery of function of the motor nerves is adequate for discharge.

Single injection nerve blocks have been commonly used for many years, with many techniques first introduced in the 1880s.[27] These techniques are typically used on large nerves supplying the extremities. The use of paravertebral blocks, first described in the early twentieth century, has received renewed interest because of utility in breast surgery. Paravertebral blocks are now used to mitigate the need for general anaesthesia or inpatient admission following these procedures. To adequately perform breast surgery, injections over multiple thoracic levels (T2-6) are required, and proper training is required to avoid the potential adverse effects such as pneumothorax or intravascular injection. Successfully performed blocks result in excellent anaesthesia, extended postoperative pain control with a general reduction in the requirement for oral opioid analgesics, decreased nausea and vomiting, and reduced cost to both the patient and the hospital.[23,28,29]

The use of a combination of lumbar plexus, femoral nerve block and sciatic nerve block for total knee replacement, has been popular. This is partly as a result of the increased use of low-molecular weight heparin by orthopaedic surgeons, raising concerns of neuraxial hematomas in patients receiving neuraxial blocks. The combined lumbar plexus, femoral and sciatic nerve block has fewer haemodynamic effects than a neuraxial block, and leaves the contralateral side unaffected. The lumbar plexus-sciatic nerve block can also be used to augment a neuraxial block or general anaesthesia in selected patients.[30] Another technique that has shown some promise is intraoperative laparoscopic intercostal nerve blocks during video-assisted thoracic surgery.[31]

To prolong the duration of postoperative analgesia, continuous regional catheters following a single injection of local anaesthetic have been increasingly used. Slight adaptations in the technique of single injection placement allow for the insertion of small catheters in larger nerve sheaths for continuous regional infusions. In ambulatory patients, these techniques are essentially limited to the upper extremity because of the potential loss of motor strength associated with a lower extremity catheter. The most common location for an upper extremity catheter is in the brachial plexus, although the approach and location may differ.

A recent European study demonstrated improved patient satisfaction in patients receiving patient controlled interscalene analgesia compared with intravenous patient controlled analgesia (PCA).[32] A new approach to the brachial plexus, the interscalenocleidomastoid approach, has been recently described. This technique would appear to decrease the rate of complications (e.g. pneumothorax) associated with the more traditional supraclavicular approach because of the tangential angle of the needle while accessing the brachial plexus.[33] An alternative to prolong the duration of analgesia is the use of patient-controlled regional anaesthetic pumps after discharge from day surgery. The extension of this anaesthetic technique into post-discharge therapy may shorten hospital stays, thus, reducing costs as well as improving analgesia.

If larger areas of anaesthesia and/or analgesia are desired, the use of a central neuraxial block may be considered. Central neuraxial blocks include intrathecal (spinal), epidural and caudal blockade. These blocks allow for major operations to be performed, including intra-abdominal procedures,

without resorting to general anaesthesia. Additionally, they have the advantage of providing an extended period of postoperative analgesia and are associated with a lower incidence of adverse events such as nausea, vomiting, sedation and deleterious effects secondary to intubation of the trachea.[3] However, compared with general anaesthesia, neuraxial blocks may be associated with a higher incidence of pruritus and urinary retention, as well as technique specific sequelae such as back pain and post dural puncture headache.

Intrathecal blockade is more commonly practised in ambulatory surgery than epidural or caudal blocks because of its greater reliability and faster onset of action. First performed in the late 19th century with local anaesthetic alone, this technique is now commonly performed with local anaesthetics, opioids, mixtures of both, or combined with other adjuvants such as epinephrine or ketamine. The use of combination medications allows for a synergistic effect as a result of individual medications acting on separate receptor types in the spinal cord. The use of a short acting opioid such as fentanyl allows for a smoother transition to oral analgesics in the postoperative period.[34] Intrathecal block enables procedures ranging from lower extremity surgery, perineal procedures to major abdominal procedures to be performed. In addition, an intrathecal block to the midthoracic level causes gut contraction due to the relative increase in activity of the vagus nerve, improving intra-abdominal surgical conditions.[27]

The epidural route of drug delivery has achieved widespread use in surgical and obstetrical anaesthesia and analgesia, and in the diagnosis and management of acute and chronic pain. The use of epidural anaesthesia and analgesia has been associated with improved outcome[35,36] and decreased requirements for inpatient stay.[37,38] Epidural blockade is usually performed in the thoracic and lumbar regions, although cervical epidural injections are sometimes prescribed for specific types of chronic pain. Caudal blockade is an epidural blockade that typically involves the sacral nerve distributions. However, because the inability to predict the effect of a single injection, and the relative delay in the set up of the block, single injection epidurals and caudal blockade are not commonly used in adult ambulatory settings.

Continuous epidural techniques have been widely used in obstetrical analgesia since the 1940s.[27] Continuous epidural delivery of local anaesthetic have been shown to improve graft patency in vascular bypass operations[39] and to provide a degree of cardiac protection in high-risk patients undergoing thoracic procedures.[40] However, the use of continuous epidural techniques in ambulatory patients is limited to situations of relative contraindications for intrathecal block, such as known predilection for postdural puncture headache with spinal anaesthesia or when the patient shows a strong preference for the technique. The catheters used in continuous epidural techniques must be removed before the patient is discharged.

Multimodal analgesia is the technique of combining multiple modalities of pain relief to provide more effective analgesia and a lower incidence of adverse effects. The use of multi-drug therapy in neuraxial blocks is one common and effective example, and may also help avoid rapid tolerance to individual medications. Multimodal analgesia encompasses the combination of different classes of pain medications to achieve better analgesia while potentially reducing adverse effects. Published studies of multimodal approaches for postoperative pain control have shown improvements in postoperative pain scores and similar reductions in analgesic requirements.[3]

1.1.3 Systemic Delivery

Pharmacological therapy should be initiated using the least invasive route that is compatible with the patient's physical state and type of surgery. While there are different routes of administration for analgesics (e.g. oral, parenteral, transmucosal, transdermal and sublingual), oral delivery of medications have remained the mainstay for postoperative pain control. The oral route is effective, the simplest to use and typically the least expensive.

Oral

Oral medications range in strength from paracetamol (acetaminophen) to opioids such as morphine.

As a rule, the strength of pain medication should match the relative intensity of the pain as well as the severity and invasiveness of the surgery. The administration of oral medications is usually not appropriate immediately postoperatively in patients who have received general anaesthesia; this is because general anaesthesia often results in impaired consciousness and postoperative nausea and vomiting, which can lead to aspiration. In patients who have received regional anaesthesia, the administration of oral pain medications should begin immediately signs that the block is receding are seen. This allows for the lag time between the administration of the analgesic and the onset of effect.

Many oral preparations are combinations of different types of analgesics, such as aspirin or paracetamol as well as an opioid of varying strength, with the aim of a synergistic effect allowing for a reduction in the total amount of opioid administered. It is worth noting that gastrointestinal absorption can vary, and that different disease states can affect the rate and extent of absorption. Some preparations will make provisions to control the location of absorption, such as enteric-coated aspirin. This coating allows aspirin to pass through the stomach and into the small intestine before dissolving. This would potentially protect the gastric mucosa from the deleterious effects of the drug.

Some oral preparations allow for a time-dependent release of the contained drug, allowing a more constant delivery of medication into the systemic circulation and the reduction of administration frequency. However, there has been some recent concern over the misuse of time-release oxycodone in the Oxycontin®[1] formulation. This tablet is a non-digestible matrix that is then filled with large amounts of oxycodone and slowly time released by diffusion out of the matrix. If the matrix is crushed and ingested, the entire drug contained in the preparation is immediately released, providing the user with a euphoric state. This preparation has also been the cause of a number of deaths due to accidental overdose. Providers should exercise caution when prescribing this medication because of its high potential for abuse.

Intramuscular

Another traditional method of delivering pain medication is via the intramuscular route. Opioid intramuscular injections are typically given every 3–4 hours. The NSAID, ketorolac can also be given intramuscularly, but with a 6-hour dose administration schedule. Intramuscular injections are delivered into large muscle bodies, either the lateral deltoid or the upper outer quadrant of the gluteus maximus. This is done to avoid neurovascular structures and because the large muscles support rapid absorption through generous blood perfusion. Intramuscular injections are typically not well tolerated by patients and should only be used when venous access is not available. The Agency for Healthcare Policy and Research Acute Pain Clinical Practice Guidelines[1] discourages intramuscular administration, as it can be painful, have wide fluctuations in the rate of absorption, result in a 30–60 minute lag time to peak effect and exhibit a rapid fall-off of action when compared with oral administration.

Intravenous

The intravenous route is recommended for the treatment of acute pain. Intravenous injections have the advantages of a rapid onset of action and easier titratibility to achieve appropriate pain relief. An administration method with a proven safety record, PCA is provided by a mechanical pump device that delivers either a patient-controlled bolus on a pre-set time delay, a steady continuous infusion of medication or both types of delivery. The prescribing practitioner determines appropriate dose limits, usually every 4 hours, for the delivery of medication. This is dependent upon age, weight, type of surgery and history of analgesic use. This technique closes the loop between the patient's symptom and the required pain relief. The administration of small, frequent, appropriately timed doses of analgesic medication allows the patient to keep the blood concentrations of the analgesic within the therapeutic window. The PCA device may be a simple

1 Use of tradenames is for product identification only and does not imply endorsement.

mechanical device or a more complex processor controlled electronic pump.

PCA is rarely used in the ambulatory setting as patients often do not stay in the hospital long enough to realise its benefits. Instead, pain control is achieved in the postoperative care unit with small, short interval doses of intravenous opioids with or without adjuncts, such as ketorolac, until the desired effect is achieved. Once the patient is comfortable, nursing staff will facilitate oral intake of fluids and, when well tolerated, oral route of administration will be commenced.

Other Routes

Other lesser-used routes of administration include nasal, rectal, topical, subcutaneous and sublingual. Many pain medications can be administered using these methods. They have advantages over oral administration in that they avoid the effects of first-pass metabolism in the liver. Preparations include a fentanyl 'lollipop' for sublingual administration and a lidocaine patch for localised topical administration. Many of these methods are also used in sedating paediatric patients before obtaining intravenous access. Iontophoretic delivery of fentanyl by patient controlled methods is currently undergoing phase III clinical trials and may prove to be effective in controlling more severe postoperative pain following discharge.[41]

1.2 Non-Pharmacological Methods

Despite the focus on pharmacological intervention for postoperative pain control, an integrative approach to postoperative pain management should be encouraged. There are several techniques that have been proven to be effective with minimal adverse effects.

Acupuncture, a form of traditional Chinese medicine, has found utility in modern western practice. Preoperative insertion of acupuncture needles at traditional acupuncture points decreased supplemental postoperative morphine consumption by 50% compared with controls in a recent study.[42] Additionally, plasma cortisol and adrenalin levels were reduced by 30–50% in the initial 24 hours postoperatively. Technology has been combined with traditional medicine by using transcutaneous electrical nerve stimulation at known acupuncture points. In a group of one hundred women undergoing lower abdominal surgery, 9–12mA of electrical stimulation was found to decrease postoperative hydromorphone requirements by 65% as well as the duration of PCA use compared with controls.[43] A follow-up study demonstrated that placing the stimulating electrodes at pre-incisional dermatomal levels was as effective as the use of traditional acupoint locations. Either of these locations was more effective than a non-acupoint location.[44]

Massage therapy has been examined in conjunction with epidural analgesia for women in labour. It was found that gentle epigastric massage caused alleviation of nausea and shortened the regression time of the sensory anaesthesia.[45] However, similar epigastric massage did not shorten the onset time of epidural sensory blockade.[46]

Another alternative therapy studied for the management of postoperative pain is the use of music during anaesthesia. The use of music therapy was associated with a decrease in sedation and opioid analgesic requirements during spinal or intravenous sedation/monitored anaesthesia care.[47] Whether this reduction in medication requirements continues into the postoperative period is unknown.

Electromagnetic millimeter waves have been used for pain control in Europe for at least a decade but are relatively unknown in the US. Millimeter waves are typically used at the frequencies of 37–78Ghz with power levels less than 25mW/cm^2. A double-blinded study conducted in healthy volunteers showed a significant suppression of pain with millimeter waves when compared with controls.[48] Further research is warranted to define its role in postoperative patients.

Hypnosis has been a topic of interest for many years. A recent meta-analysis of 20 independent controlled studies showed that almost 90% of patients benefited from the use of hypnosis when compared with controls using six different outcome parameters, including pain scores and the amount of pain medication used.[49] This suggests that hypnosis

may have important benefits for patients willing to embrace this alternative modality.

2. Analgesic Drug Classes for Postoperative Pain Management

The choices of intravenous analgesics may be broadly divided into opioids and non-opioids. While opioids remain the mainstay for treating most postoperative pain, combinations of medications may prove to be more efficacious. Many studies have demonstrated improved pain relieve when opioids are combined with NSAIDs in the early postoperative period.[3] If the level of pain is less severe, non-opioid analgesics may be used.

Paracetamol is an over-the-counter analgesic that is used widely for the treatment of mild to moderate pain. Many medications contain paracetamol in combination with other analgesics. Usually administered via the oral or rectal route, paracetamol is equivalent to aspirin in strength and causes pain relief by elevating the pain threshold.[50,51] The maximum recommended daily dosage is 4000mg in adults and this should be decreased in patients with a history of heavy alcohol use.[50] If used over a long-term period, in large doses, in combination with alcohol or in intentional overdose, paracetamol can cause liver toxicity or even liver failure.

2.1 NSAIDs

NSAIDs are the largest group of non-opioid analgesics. Aspirin or acetylsalicylic acid is the first NSAID medication used clinically. Originally obtained from tree bark, aspirin is widely used as an analgesic but has potential adverse effects. Aspirin can cause gastrointestinal bleeding because of its erosive effect on the gastric mucosa and because of its irreversible effect on platelet function. A single dose of aspirin will effectively deactivate circulating platelets by permanently inhibiting platelet production of thromboxane A_2. This side effect is desirable in treating patients with occlusive cardiovascular disease but may increase postoperative bleeding. Other NSAIDs, such as ibuprofen or naproxen, have similar antiplatelet effects but these are transient in nature.

NSAIDs are divided into several groups depending upon their chemical characteristics. Perhaps the most commonly used are the propionic acid derivatives (such as ibuprofen and ketoprofen), several of which are now available over-the-counter in the US. These medications inhibit cyclo-oxygenase (COX) enzymes involved in the synthesis of prostaglandins. An increased synthesis of prostaglandin (PG)E_2 and PGI_2 occurs during tissue injury and inflammation. This results in sensitisation of pain-transmitting C fibres by lowering their threshold to noxious stimuli, including the trauma of surgery.[51] Ketorolac is the only NSAID currently available for parenteral use and is limited to 5 days of use. Administered before incision, it has been found to decrease the postoperative morphine requirements in major orthopaedic surgery[52,53] and in diagnostic laparoscopy,[54] although adverse effects such as bleeding[55] and possible renal effects[56] can limit its application. It is relatively contraindicated in patients with impaired renal function, asthma, allergies, bleeding disorders, and a history of peptic ulcers and in patients taking aspirin.

2.2 Cyclo-Oxygenase-2 Inhibitors

COX has recently been found to possess two isoenzymes, designated as COX-1 and COX-2. The older generation of NSAIDs are non-specific inhibitors, causing inhibition of both the COX-1 and COX-2 enzymes. The inhibition of COX-1 causes undesirable adverse effects in the gastrointestinal tract and the platelets. Conversely, COX-2 inhibition appears to be responsible for the reduction of inflammatory responses and hence the therapeutic effects of analgesia[57] (see figure 1).

Two US FDA approved medications for acute postoperative pain, celecoxib and rofecoxib are specific COX-2 inhibitors, and have gastric and platelet sparing effects. Under investigation is an injectable COX-2 inhibitor, parecoxib, which is an intravenously administered prodrug that is converted to valdecoxib *in vivo*. Parecoxib has also been demonstrated to have gastric[57] and platelet[58] sparing effects, and has analgesic potency equivalent to ketorolac. This medication has multiple advantages,

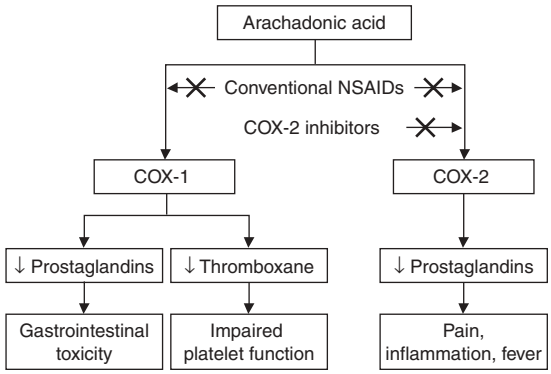

Fig. 1. NSAID mechanism of action. **COX** = cyclo-oxygenase.

including administration intraoperatively and immediately postoperatively before oral medications would be tolerated. Preliminary data suggests that the efficacy of parecoxib 40mg is equivalent to that of ketorolac 30mg in dental, orthopaedic and gynaecological surgery.[59-61] This medication is in late phase III clinical trials and should be available commercially in the US in the next 1–2 years.

2.3 Opioids

Moderate to severe pain, unresponsive to non-opioids will generally require the addition of opioids to pain medication regimens. Opioids have been used therapeutically since the discovery of opium, the dried sap of the opium poppy. Although not used for therapeutic purposes today, its derivative, morphine, is the standard to which all other opioids are measured. The term opioid differs from opiates, in that opiates include only natural derivatives of opium, while opioids includes all natural, semi-synthetic and fully synthetic compounds which have opium-like effects. This includes endogenous opioids such as endorphins. These compounds act directly on receptors in the central nervous system, producing a moderate to strong analgesic effect, along with the potential for deleterious effects such as respiratory depression, constipation, euphoria, drowsiness, nausea, vomiting, and eventually tolerance and physiological and physical addiction. Opioids can be subdivided into agonists, antagonists or agonist-antagonists, although pure antagonists have no analgesic effect.

Opioid agonists have pharmacological effects that are similar to morphine. These compounds range in strength from those appropriate for moderate pain, such as oxycodone and hydrocodone to potent opioids used intraoperatively, such as fentanyl, alfentanil, sufentanil and remifentanil. There are three major subtypes of opioid receptor, mu (μ), kappa (κ), and delta (δ), with several other variants of sub types described. The opioid agonists have agonistic activity at all three receptor types, with individual affinities determining efficacy and adverse effect profiles. One study compared fentanyl with morphine postoperatively in ambulatory patients.[34] Morphine appeared to provide more effective pain control in the post anaesthesia care unit, but also caused more frequent nausea and vomiting after discharge. Additionally, respiratory depression is the most serious of the opioid agonist adverse effects.

Agonist-antagonist opioid medications are opioids that show selective agonist receptor activity. These compounds may have agonist stimulatory effects at one receptor while antagonistic effects at another. In addition, these medications typically exhibit a ceiling effect, not only with respect to their analgesic effect but also in the degree of respiratory depression. Beyond the doses needed to produce this ceiling effect, these medications are ineffective. If given after or in conjunction with pure agonist drugs, these medications can reverse the effects of the agonists or actually precipitate withdrawal symptoms. Because of an increase in adverse effects, and the limitations of the therapeutic effect, the postoperative use of these medications is limited.

2.4 Novel Analgesics

Other adjuvant medications have been explored for postoperative use. Ketamine, a phencyclidine derivative first synthesised in 1963, acts on the NMDA receptor, which is known to facilitate pain processing. When combined with opioids, ketamine reduces opioid consumption and improves analgesia. It can be administered either intravenously or epidurally.[62]

Flumazenil, a benzodiazepine antagonist, was given in combination with morphine postoperatively in patients undergoing inguinal herniorrhaphy and was found to decrease morphine consumption compared with morphine alone.[63] The mechanism of action of flumazenil is unknown but several hypotheses have been proposed. One possible mechanism is via the release of endogenous opioids. Another possibility is thought to be through $GABA_A$ receptors. In addition, cognitive, haemodynamic and respiratory functions were improved in the group given both morphine and flumazenil.[63]

Lidocaine, when given intravenously in the preoperative and intraoperative periods to patients undergoing radical retropubic prostatectomy, was found to not only decrease postoperative pain, but to also decrease the period of postoperative ileus and shorten hospital stay.[64] Recent studies found that small doses of continuous infusion of naloxone (0.25 μg/kg/h) or nalmefene (15–25μg) were effective in reducing opioid related adverse effects, and paradoxically reduced postoperative opioid requirement and improved analgesia.[65,66]

An adaptation of the WHO's analgesic ladder may be useful to tailor the analgesic to the anticipated level of pain (figure 2). An integrated therapy regimen combining analgesic and non-pharmacologic methods is presented in figure 3.

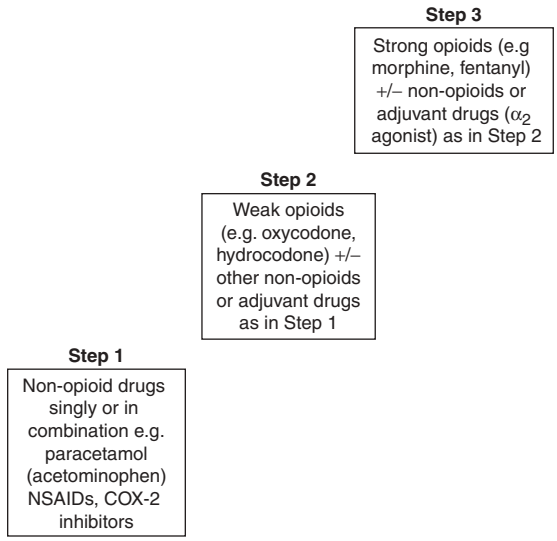

Fig. 2. Adaptation of the WHO analgesic ladder to help tailor the analgesic to the anticipated level of postoperative pain in patients undergoing ambulatory surgery. **COX-2** = cyclo-oxygenase-2.

3. The Influence of Psychosocial Aspects and Patient Characteristics on Postoperative Pain Management

The psychological aspects of pain control should not be dismissed. Pain is not just a sensation but also has an emotional component. Nociceptive signals produce extensive emotional processing in the limbic system.[67] This is an evolutionary survival tactic in that this negative emotion fosters adaptive behaviour to avoid a repetition of the stimulus. The emotional component of pain is then proportional to the perceived physical significance of the injury, whether from a predator or a therapeutic operation. Perception in the subjective interpretation of pain is dependent upon a host of social, environmental and psychological factors that vary among individuals. Psychosocial issues may complicate the emotional component of pain but also allow opportunities for controlling this component.

The past experiences of a patient may have a profound effect upon the perception of present events. Current emotions may trigger the memory of events that were originally coded into long-term memory during a similar emotion. For example, preoperative anxiety may allow stronger recall of similar anxieties experienced in the past, especially when the postoperative pain from the previous experience was inadequately controlled. This could then predispose the patient to inadequate pain control during the current experience. The practitioner should explore alternatives that allow patients to effectively cope with emotions generated during the preoperative period. One method is to allow the patient to perceive some modicum of control in their therapy. For example the use of PCA devices, such as intravenous opioid pumps or incisional local anaesthetic pumps changes the patient's role from passive to active.[67] This can also be accomplished by allowing some flexibility in oral pain medication dose administration and scheduling. The loss of self-determination can be very demoralising, especially

in elderly patients, and even a small degree of self-determination will avoid feelings of helplessness.

4. Conclusion

Postoperative pain control is a wide-ranging and complicated subject involving a cornucopia of therapies and treatments. Patient education, early diagnosis of symptoms and aggressive treatment of pain using an integrative approach, combining pharmacotherapy as well as complementary technique, should serve us well in dealing with this complex problem. Most importantly, the practitioner needs to possess one quality that was advocated by Hippocrates: empathy.

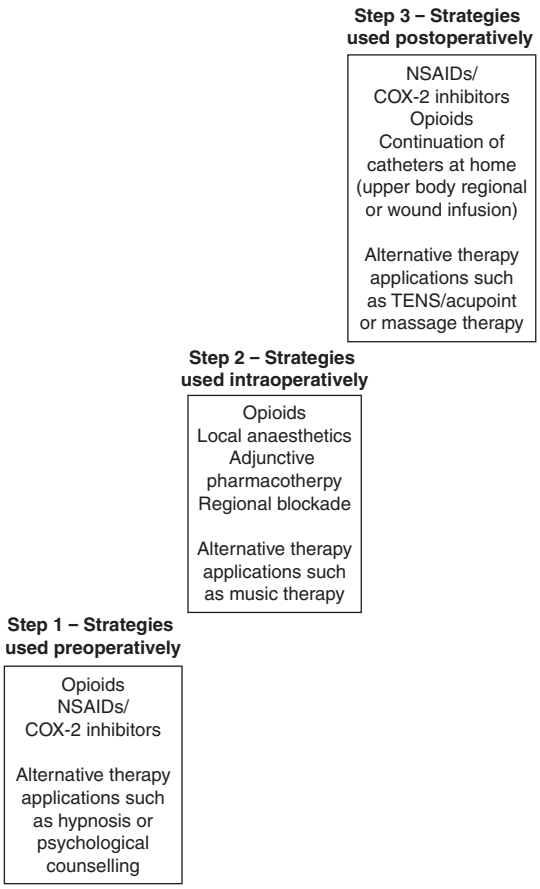

Fig. 3. An integrated therapy regimen combining analgesic and non-pharmacological methods for use in patients undergoing ambulatory surgery. **COX-2** = cyclo-oxygenase-2; **TENS** = transcutaneous electrical nerve stimulation.

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