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REVIEW

Recent Advances in Postoperative Pain Management

Nalini Vadivelu, MD[a*]; Sukanya Mitra, MD[b]; and Deepak Narayan, MD[c]

Departments of [a]Anesthesiology and [c]Surgery, Yale University School of Medicine, New Haven, Connecticut, and [b]Department of Anaesthesia & Intensive Care, Government Medical College & Hospital, Chandigarh, India

Good pain control after surgery is important to prevent negative outcomes such as tachycardia, hypertension, myocardial ischemia, decrease in alveolar ventilation, and poor wound healing. Exacerbations of acute pain can lead to neural sensitization and release of mediators both peripherally and centrally. Clinical wind up occurs from the processes of N-Methyl D-Aspartate (NMDA†) activation, wind up central sensitization, long-term potentiation of pain (LTP), and transcription-dependent sensitization. Advances in the knowledge of molecular mechanisms have led to the development of multimodal analgesia and new pharmaceutical products to treat postoperative pain. The new pharmacological products to treat postoperative pain include extended-release epidural morphine and analgesic adjuvants such as capsaicin, ketamine, gabapentin, pregabalin dexmetomidine, and tapentadol. Newer postoperative patient-controlled analgesia (PCA) in modes such as intranasal, regional, transdermal, and pulmonary presents another interesting avenue of development.

Proper pain relief is a major concern and area of focus in the United States today. Pre-operatively, one of the most common questions asked by patients pertains to the amount of pain they will experience after the surgery. Pain is also one of the primary concerns of the surgeon because of its close ties with clinical outcome and acute postoperative patient well-being. Studies have indicated such negative clinical outcomes to include decreases in vital capacity and alveolar ventilation, pneumonia, tachycar-

*To whom all correspondence should be addressed: Dr Nalini Vadivelu, Department of Anesthesiology and Surgery, Yale University School of Medicine, New Haven, CT 06511; E-mail: nalini.vadivelu@yale.edu.

†Abbreviations: NMDA, N-Methyl D-Aspartate; LTP, long-term potentiation; PCA, patient-controlled analgesia; BK, bradykinin; 5HT, 5 hydroxytryptamin; CGRP, calcitonin gene-related protein; AMPA, amino-3-hydroxyl-5-methyl-4-proprionic acid; KAR, Kainate; EPSP, excitatory postsynaptic potentials; NO, nitric oxide; SO, superoxides; NK1, neurokinin receptor; COX-2, cycloxygenase 2; EREM, extended-release epidural morphine; fentanyl ITS, fentanyl hydrochloride iontophoretic transdermal system; FDA, U.S. Food and Drug Administration; IV, intravenous; MAOI, monoamine oxidase inhibitors; PCRA, patient-controlled regional analgesia; RM, ropivacaine/morphine; RMK, ropivacaine/morphine/ketorolac; IN, intranasal; PCINA, patient-controlled intranasal analgesia; NNT, number-needed-to-treat; IA, intraarticular.

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dia, hypertension, myocardial ischemia, myocardial infarction, transition to chronic pain, poor wound healing, and insomnia [1,2,3].

Pain has been found to be one of the three most common medical causes of delayed discharge after ambulatory surgery, the other two being drowsiness and nausea/vomiting. Despite this overwhelming rationale for effective postoperative pain control, the clinical reality is, unfortunately, still far from satisfactory. As a recent editorial title suggests, we have a long way to go to achieve satisfactory postoperative pain control [3]. In an often-cited study [4] that assessed patients' postoperative pain experience and the status of acute pain management in a random sample, approximately 80 percent of patients said they experienced acute pain after surgery. The authors concluded that despite an increased focus on pain management programs and the development of new standards for pain management, many patients continue to experience intense pain after surgery.

During the last couple of decades and especially the last few years, major technological breakthroughs that have the potential to significantly advance the field of postoperative analgesia have occurred and are still underway. This article discusses some of the more important of these recent advances. We focus on the developments particularly over the last five years.

There are several strands of development that overlap, and it is difficult to do justice to this burgeoning area within the scope and limits of this article. This review will outline the main directions of this development and dwell upon a few selected recent ones in some detail.

The recent advances in postoperative pain management can be loosely grouped in the following areas:

- Molecular Mechanisms
- Pharmaceutical products
- Routes and modes of delivery
- Other modes of analgesia
- Organizational and procedural aspects

MOLECULAR MECHANISMS

It is important to know about the recent advances in central sensitization since it plays an important role in post surgical and post traumatic pain [5,6]. Postoperative pain is mostly nociceptive, which is pain perception following surgical insult.

However, there can be exacerbation of acute nociceptive pain leading to neural sensitization when sensations that are not normally painful are perceived as painful, as in hyperalgesia and allodynia. Mechanical allodynia occurs due to the release of several primary and secondary noxious sensitizers such as PGEs, leukotrienes [7], bradykinin (BK), histamine, and 5 hydroxytryptamine (5HT). These conditions are commonly seen in those patients developing neuropathic pain. Primary hyperalgesia occurs when there is sensitization of peripheral nociceptors, while secondary hyperalgesia is associated with the sensitization of the spinal cord and the central nervous system.

In peripheral sensitization, there is a release of primary mediators such as prostaglandins, 5 hydroxytryptamine, leukotrienes, and bradykinins. These primary mediators stimulate the release of peptides such as calcitonin gene-related protein (CGRP) [8], substance P [9], and cholecytokinin [10] at the site of injury. Histamine-induced vasodilatation, nerve growth factor release, and reflex sympathetic efferent release of norepinephrine are other processes related with peripheral sensitization.

Impulses from the peripheral nociceptors travel via A delta and C fibers to synapse in the lamina II and lamina V of the spinal cord. C fibers also synapse in the lamina I of the spinal cord.

The second order neurons of the spinal cord are of two types: the first, in lamina I, responds to impulses from the C fibers; the second is the wide dynamic range neuron located in lamina V that responds to both noxious and non noxious stimuli. Neurotransmitters such as glutamate and aspartate present in lamina V produce fast synaptic transmission. They do so by binding and activating amino-3-hydroxyl-5-methyl-4-proprionic acid (AMPA) and

Kainate (KAR) receptors that regulate Na+ and K+ ion influx. AMPA and KAR are almost impervious to Ca++ ions. Once the AMPA and KAR receptors are activated, they start the priming of NMDA, which is voltage mediated [11].

NMDA receptor and central sensitization

NMDA is a membrane protein that regulates the flow of Na+ and Ca++ into the cell and the outflow of K+ outside the cell by an ion channel present intrinsically. The NMDA receptor is made up of four subunits: two NR1, one NR2A, and one NR2B. Each of these has a cytoplasmic portion outside the cytoplasm that can be allosterically modified by zinc ions.

NMDA receptors require ligand binding with glutamate and aspartate and AMPA-induced membrane depolarization and a positive change in the voltage inside the cell. This makes NMDA receptors ligand dependent and voltage gated. Activated AMPA receptors produce a depolarization that dislodges a magnesium plug from the ion channel of the NMDA receptor. The removal of the magnesium plug initiates the entry of calcium ions into the neuronal. Direct action of glutamate at the glutamate binding site further sensitizes the channel [12].

As intracellular calcium accumulates, a chain of neurochemical and neurophysiologic changes leads to the rapid and independent firing of spinal neurons without stimulation. This process is termed as "*wind up*," which is the excitation of the dorsal horn neurons not dependent on transcription of specific genes.

Long-term potentiation of pain

Clinical hyperalgesia occurs from the processes of NMDA activation, wind up, and central sensitization [13]. Central sensitization can occur in the spinal cord as well as in the supraspinal regions of the central nervous system, such as anterior cingulate gyrus, amygdale, and rostroventral medulla. Activation of the NMDA in the spinal cord and the supraspinal areas and increased neuronal calcium ion (Ca++) influx lead to wind up and early LTP [14] of pain that is transcription independent in the induction phase. Long-term potentiation of pain increases the excitatory postsynaptic potentials (EPSP) involved in chronic pain.

Transcription-independent and transcription-dependent central sensitization

Central sensitization can be transcription dependent and transcription independent. Both activation of NMDA wind up and early LTP of pain are transcription-independent processes. There is increasing pain with each repetitive stimulation [15]. The transcription-independent process is heterosynaptic central sensitization, in which low threshold A Beta input elicit responses after C fiber conditioning. Wind up and early LTP are reversible processes.

Transcription-dependent sensitization occurs in prolonged noxious facilitation leading to the activation of genes, mRNA transcription, and subsequent translation into modified proteins. Excitotoxicity occurs from increased influx of Ca++ with resultant increase in prostaglandins PGE, nitric oxide (NO), and superoxides (SO). Transcription-dependent sensitization affects the spinal cord and other areas within the central nervous system. It is now thought that transcription-dependent sensitization is mediated by inflammation and related alterations in the dorsal root ganglion, the dorsal horn, and irreversible structural modifications in the central nervous system [16]. Transcription-dependent sensitization can take two forms: activity independent localized form, which includes the late phase of LTP, and the activity independent widespread form. Late phase LTP has been studied mainly in the hippocampus and other cortical areas [11].

Common mechanisms of pain and memory

It has been seen that the neurokinin receptor (NK1) and cycloxygenase 2 (COX-2) are involved in central sensitization. The genes for Dynorphin and NK1 have been seen to be upregulated in the spinal cord, and widespread COX-2 has been seen to be upregulated in many areas of the central

nervous system by pain facilitation [11]. However, NK1 and COX2, which are involved in central sensitization, are not involved in hippocampal LTP. It is also known that NMDA receptors, essential for activity dependent central sensitization, also are necessary for the initiation of LTP, which has a role in the consolidation of memory. The common mechanisms in hippocampal early phase LTP and central sensitization are phosphorylation of synaptic receptors and the insertion of AMPA receptors into the post-synaptic membrane. There is only synaptic strengthening in hippocampal LTP, while central sensitization also can cause neuronal network changes and other cellular mechanisms. It is necessary then to avoid the interruption of memory formation and cortical function while treating central sensitization since the process of LTP is present in central sensitization as well as in memory mechanisms in the cortex [11].

Advances in knowledge of the molecular mechanisms of pain have led to development of multimodal analgesia and new pharmaceutical products to treat pain. We will highlight the important recent advances in pharmaceutical products and the routes through which they can be given, as well as important non-pharmacological advances in pain control that are useful for health care personnel treating postoperative pain. Non-pharmacological advances in analgesia are exemplified by application of acupuncture, and related therapies for postoperative pain control will be discussed. In addition, drug tolerance in patients with illicit drug use or a history of taking high doses of pain prescription medications prior to admission are making postoperative pain management a challenge and warrants discussion as well.

ADVANCES IN PHARMACEUTICAL PRODUCTS

The two most important new products are extended-action epidural morphine and iontophoretic transdermal fentanyl. Others include the use of various non-analgesic substances as adjuvants, major examples being ketamine and some anticonvulsants (notably gabapentin). There is also a renewed interest in judicious use of cyclooxygenase inhibitors (coxibs). Long-acting preparations of local anesthetics constitute another area of ongoing research.

Newer PCA in modes such as intranasal, regional, transdermal, and pulmonary presents an interesting avenue of development.

Multimodal analgesia

The concept of multimodal analgesia first proposed about 15 years ago is now quite well established in clinical practice. For example, non-steroidal anti-inflammatory medications combined with intravenous patient-controlled morphine administration may decrease nausea and sedation in patients when compared with those using patient-controlled morphine alone [17]. Different classes of analgesics using different routes of administration such as intravenous and epidural are used to produce fewer side effects of sedation, nausea, vomiting pruritis, constipation, and improved pain relief. Multimodal analgesia also can produce opioid sparing. Other studies have shown, however, that multimodal analgesia may not improve postoperative outcome significantly. Faster recovery, reduced hospital stay, and decreased length of convalescence can occur if multimodal analgesia is combined with a rehabilitation program that is multidisciplinary and multimodal [18]. The development of newer agents available for postoperative pain control opens up possibilities for newer combinations in multimodal analgesia.

Extended-release epidural morphine

The goal of current postoperative pain research and development is to find a medication that can work locally to give long-lasting pain relief at the site of surgical focus. The new drug, a single-dose, extended-release epidural morphine (EREM) called DepoDur™, may be a step toward this analgesic goal. When clinically applicable, the use of DepoDur™ has been found to have a duration of action up to 48 hours [19,20] with long-lasting analgesia in the absence of large systemic concentrations of opioids as well as better patient activity levels.

EREM is formulated for a one-time dose, given epidurally at the lumbar level. DepoDur™ has been evaluated in such surgeries as knee arthroplasty and cesarean section. Several studies have shown that EREM produces long-term pain relief [8-10].

Side effects of EREM have been treated with opioid antagonists. Twelve to 12.5 percent of patients who received EREM required opioid antagonists [19,20]. It has been stated that pruritis [19] and respiratory depression [20] were the primary causes for antagonist administration. The elderly are particularly sensitive to the effects of EREM and require close perioperative monitoring. It was shown that the elderly treated with 15 mg of EREM had equivalent fentanyl usage as younger patients treated with 20 mg of EREM [21]. Attentive perioperative monitoring is needed for elderly patients.

Fentanyl iontophoretic transdermal system

Although PCA has demonstrated efficacy and patient satisfaction, current techniques using intravenous (IV) administration present limitations, including the risk of programming errors and the potential to limit patient mobility due to pumps, lines, and tubing. The patient-controlled fentanyl hydrochloride iontophoretic transdermal system (fentanyl ITS) was designed to address these concerns [22]. Fentanyl ITS is an innovative, needle-free, self-contained, pre-programmed drug-delivery system that uses iontophoretic technology to deliver fentanyl through the skin by application of a low-intensity electrical field [23,24,25]. It has not been approved by the U.S. Food and Drug Administration (FDA) for current clinical use; however, clinical studies have been conducted on human subjects to evaluate it for efficacy, safety, and tolerability.

Efficacy of fentanyl ITS

The efficacy of fentanyl ITS in treating acute postoperative pain was first established in three phase 3 double-blind placebo-controlled clinical trials [26,27]. More importantly, fentanyl ITS now has been demonstrated to have efficacy and safety equivalent to morphine IV-PCA in four randomized controlled trials [28,18], a subgroup analysis [29], and a meta-analysis [30]. It is thought that 40 percent of the administered dose is absorbed in the first hour of treatment and the system reaches 100 percent efficacy in 100 hours.

Panchal et al. [31] evaluated the incidence of analgesic gaps resulting from system-related events (SREs) for patients using the fentanyl ITS vs. morphine IV PCA for postoperative pain management. Fentanyl ITS was associated with a significantly lower incidence of analgesic gaps than morphine IV PCA.

Safety and tolerability of fentanyl ITS

The safety and tolerability of fentanyl ITS have been found to be acceptable by several studies and pooled data analysis [32]. Adverse events associated with fentanyl ITS are similar to those reported with IV opioid administration, including nausea, vomiting, pruritis, headache, and mild-to-moderate dizziness. Nausea was the most common adverse event, with the incidence ranging between 26.6 percent and 67.5 percent [27,28,33].

Disadvantages

As with all transdermal systems, skin hypersensitivity, skin redness, and hyperpigmentation are potential problems. The system has not been adequately studied in children. It should be used with extreme caution for in-patients with severe hepatic dysfunction, head injuries, sleep apnea, and impending respiratory failure and in patients with increased intracranial pressure of any etiology.

The system lacks programmability and a basal infusion rate that may be important in opioid-dependent and opioid-tolerant patients. The number and timing of attempts by the patient also cannot be determined. The system has to be disposed only after disassembly by the pharmacist. The most important disadvantage at the current time is the availability of fentanyl ITS, since it is not currently being produced due to techni-

cal problems. Perhaps technological modifications, including recording the number and timing of the attempts and the addition of a basal rate, may make it more advantageous in the future.

ANALGESIC ADJUVANTS

Adjuvants are compounds, which by themselves have undesirable side effects or low potency but in combination with opioids allow a reduction of narcotic dosing for postoperative pain control. Adjuvants are needed for postoperative pain management due to side effects of opioid analgesics, which hinder recovery, especially in the increasingly utilized ambulatory surgical procedures [34]. Multiple adjuvanta recently have been developed for the control of pain.

Capsaicin

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a non narcotic and acts peripherally. It acts as a TRPV-1 agonist [35]. TRPV1 is a receptor that is markedly reduced in inflammatory conditions and is present on unmyelinated C fiber endings in the periphery. The activation of the TRPV receptors releases high intensity impulses and releases substance P, which results in the initial phase of burning. Continued release of substance P in the presence of capsaicin leads to the depletion of capsaicin and a subsequent decrease in C fiber activation. It is important to remember that capsaicin does not produce significant effects on the A delta and A alpha fibers and does not affect the temperature and touch sensations.

It can be used as a cream and also as an injectable analgesic. It is not an FDA approved product but is currently in Phase 3 trials for postoperative pain control, arthritis, musculoskeletal pain, and chronic neuropathic pain. Capsaicin is present in high concentration in the seeds and stem of chili peppers. It is an alkaloid.

Capsaicin cream contains capsaicin that is usually combined with narcotic analgesics and NSAIDS to relieve a variety of painful ailments such as back pain, arthritic joint pains, and strains and sprains. Capsaicin cream is also used in higher concentrations for the treatment of the neuropathic pain of post herpetic neuralgia. It can be used in the elderly as an adjuvant, as it is thought to have opioid sparing effects. This can be particularly beneficial for the elderly who are sensitive to respiratory depression that can occur with opioids.

Injectable capsaicin is used for the control of post operative pain, such as after total knee replacement, total hip replacement, hernia repair [36], shoulder arthroscopy, and bunionectomy. It also has uses in more long-term pain such as that due to intedigital neuromas, osteoarthritis of the knee, and neuropathic pain occurring after surgery or trauma. Pre-administration of neural blockade before injection of capsaicin may greatly decrease the burning discomfort.

Capsaicin appears to be a relatively safe drug with the only absolute contraindication being patient hypersensitivity. Relative contraindications include age less than 2 years, patients with elevated liver enzymes, patients on ACE inhibitors, and patients showing signs of septic arthritis and joint infections.

Ketamine

NMDA receptor antagonists, and specifically ketamine commonly used in clinical practice, have been used in perioperative pain management. Routes of administration include intravenous, subcutaneous, epidural, transdermal, and intra-articular. At low sub anesthetic doses (0.15–1 mg/kg), ketamine exerts a specific NMDA blockade and, hence, modulates central sensitization induced both by the incision and tissue damage and by perioperative analgesics such as opioids.

There has been a renewed interest in the use of sub-anesthetic doses of ketamine as an adjunct to provide postoperative pain relief in opioid-dependent patients [37]. There is a definite role of ketamine in preventing opioid-induced hyperalgesia in patients receiving high doses of opioid for their postoperative pain relief [38]. However, clinical use of ketamine can be limited due to psychotomimetic adverse effects such as hallucinations and bad dreams.

Other common adverse effects are dizziness, blurred vision, and nausea and vomiting [39].

Gabapentin and pregabalin

Gabapentin is an anti-epileptic drug that has demonstrated analgesic effect in diabetic neuropathy, post-herpetic neuralgia, and neuropathic pain. Gabapentin does not bind to GABA A or GABA B receptor but to the alpha-2 delta subunit of the presynaptic voltage gated-calcium channels responsible for the inhibition of the calcium influx. The inhibition of calcium release then prevents the release of excitatory neurotransmitters involved in the pain pathways. Most of the studies of gabapentin (and occasionally its structural analog pregabalin) in the perioperative setting have been published in the last three to four years, and several systematic reviews on the subject are available [31,39].

Most of the reviews and meta-analyses concur that perioperative gabapentin helps to produce a significant opioid-sparing effect and probably also improves postoperative pain score relative to the control group [40]. Tiippana et al. [41] found that the opioid-sparing effect during the first 24 hours after a single 300 to 1,200 mg dose of gabapentin, administered one to two hours preoperatively, ranged from 20 percent to 62 percent. Gabapentin and similar drugs seem to have a strong potential for perioperative use as an analgesic adjuvant and anti-hyperalgesic agent when used in conjunction with opioids.

Pregablain

Recent years also have witnessed a heightened research interest in the analgesic, sedative, anxiolytic, and opioid-sparing effects of pregabalin (S+ 3-isobutyl GABA), a structural analog of GABA and a derivative of gabapentin, in various pain settings, including postoperative pain. Its mechanism of action is thought to be probably similar to that of gabapentin but has a superior pharmacokinetic profile [42]. Pregabalin has an established efficacy of varying degree in neuropathic pain conditions such as postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia. While some studies do not demonstrate a significant analgesic effect in the acute, including postoperative, pain scenario [43], other studies suggest pregabalin to have effective sedative [44] and opioid-sparing effects [45,46], useful characteristics for the control of acute pain. Research on its established role as an analgesic adjuvant as a part of multimodal analgesia for acute pain control is ongoing. Opioid sparing effects and improved pain scores have been seen after abdominal and pelvic surgery. Its many potential actions such as reducing opioid requirements, prevention and reduction of opioid tolerance, improvement of the quality of opioid analgesia, decreased respiratory depression, relief of anxiety, and gastric sparing make it an attractive drug to consider for control of pain in the post operative period [47].

Dexmedetomidine

Dexmedetomidine is a relatively new, highly selective central alpha2 agonist. Its sedative, pro-anesthetic, and pro-analgesic effects at 0.5-2 micrograms/kg given intravenously stem mainly from its ability to blunt the central sympathetic response by as yet unknown mechanism(s). It also minimizes opioid-induced muscle rigidity, lessens postoperative shivering, causes minimal respiratory depression, and has hemodynamic stabilizing effects. Dexmedetomidine, when used as an adjunct, can reduce postoperative morphine consumption in various surgical settings using various routes such as intravenous [48,49]. A recent study has shown the analgesic efficacy of dexmedetomidine in postoperative pain relief. The authors of this study found that the addition of dexmedetomidine to IV PCA morphine resulted in superior analgesia, significant morphine sparing, and less morphine-induced nausea, while it was devoid of additional sedation and untoward hemodynamic changes [49].

OTHER RECENT ADVANCES IN PERIOPERATIVE PHARMACOTHERAPY

Local anesthetics

To effectively respond to the issue of sending the ambulatory patient home in a pain-

free state, one has to have methods to provide several days of effective and safe relief of moderate to severe pain for the unmonitored patients at home. It is clear that local anesthetic techniques, particularly peripheral nerve blockade, will be one of the cornerstones of postoperative pain management [50].

There are basically two overarching approaches for prolongation of local anesthetic action. One is the use of novel delivery techniques for existing drugs. In an endeavor to "make old drugs new" [51], liposome or polymer encapsulation of local anesthetics are being formulated. The second approach is the development of novel, extremely long-acting local anesthetics.

Liposomes are microscopic phospholipid-bilayered vesicles that are biocompatible, biodegradable, and non-immumnogenic. Recently, substantial interest has been shown in developing drug delivery systems utilizing nanoparticles, micro-particles composed of biodegradable polymers. They have some advantages over liposomes in terms of stability both during storage and *in vivo*.

To date, many local anesthetics (most commonly bupivacaine, but also mepivacaine, ropivacaine, lidocaine, prilocaine, etc.) have been loaded in liposomes or polymer microspheres [52,36]. It is hoped that in the near future, some of these formulations will become a part of the pain clinician's armamentarium. However, the road toward achieving this goal may be long and winding, due to problems of these drug delivery systems, such as shelf life, aggregation, leakage, and toxicity [53].

Renewed interest in NSAIDs and coxibs and acetaminophen

A recent review highlights current advances in our understanding of the role perioperative NSAIDs have on modulating nociception, their benefits when utilized as components of a multimodal analgesic regimen, and potential deleterious cardiovascular and estrogenic effects. Recent research indicates that, in addition to peripheral blockade of prostaglandin synthesis, central inhibition of cyclooxygenase-2 may play an important role in modulating nociception. Although nonspecific NSAIDs provide analgesic efficacy similar to coxibs, their use has been limited in the perioperative setting because of platelet dysfunction and gastrointestinal toxicity. Coxibs may be a safer alternative in that setting. Both coxibs and traditional NSAIDs may contribute to a dose-dependent increase in cardiovascular toxicity and impaired osteogenesis. When used short term at the lowest effective dose, however, NSAIDs may provide for analgesic benefit without significant toxicity.

The potential benefits of coxibs include [18] improved quality of analgesia; reduced incidence of GI side effects vs. conventional NSAIDs; and no platelet inhibition. Acetaminophen is antipyretic and analgesic but has little, if any, anti-inflammatory action. Its analgesic efficacy is not more than that of traditional analgesics; however, it has fewer side effects. The mechanism of action has been debated. In animal models, it has been seen to inhibit COX-3. At the spinal cord level, it has been shown to antagonize neurotransmission by NMDA, substance P, and nitric oxide pathways. Preparation of intravenous (IV) acetaminophen recently has been released in the United Kingdom and Europe (Perfalgan®, Bristol Meyers Squibb, New York). It is dissolved in mannitol and pH-buffered by disodium phosphate, with cysteine added as an anti-oxidant. A 100 ml solution is presented as 10 mg/ml for administration over a period of 15 minutes. The onset of action is within five to 10 minutes, with the peak at one to two hours. Optimal analgesia for moderate to severe postoperative pain cannot be achieved using a single agent alone, but a balanced approach in combination with non-steroidal agents can result in up to a 40 to 50 percent reduction in opioid requirements. IV propacetamol (1 g), a prodrug of acetaminophen, has been shown to be as efficacious as intramuscular morphine (10 mg) following dental extractions [54] and as effective as intramuscular ketorolac (30 mg) following lower limb arthroplasty [55]. With its inherent safety and demonstrated efficacy, IV acetaminophen can prove to be an asset in managing perioperative pain, especially of mild to moderate severity.

Other agents

Other non-opioid analgesic adjuvants include clonidine, neostigmine, tapentadol, and, recently, adenosine [56], though further research is necessary to establish their clinical efficacy. Of these, the use of low doses of clonidine proved to be a useful adjunct analgesic when given neuraxially and in combination with peripheral nerve blocks. Data about the systemic administration of clonidine could support the usefulness of low-dose IV administration [57].

Tapentadol

Combination analgesics that have moderate opioid efficacy and central adrenergic analgesic effects (e.g., tapentadol) have been found to provide analgesic effects similar to more potent opioids but with a lower adverse event profile. Recently, tapentadol has been approved in the United States as immediate release oral preparations of 50 mg, 75 mg, and 100 mg (Nucynta®, Johnson & Johnson) to be used every four to six hours, depending on pain intensity, with a maximum daily dose of 600 to 700 mg. Tapentadol was approved by the FDA in November 2008 for the treatment of moderate to severe pain in patients 18 years or older. Tapentadol is a centrally acting analgesic with a unique dual mode of action as an agonist at the μ-opioid receptor and as a norepinephrine reuptake inhibitor [58,59].

Tapentadol has an 18-fold affinity for the μ opioid receptor in humans as compared to morphine but is about two- to three-fold less potent than morphine, most likely because it is a norepinephrine reuptake inhibitor. It has improved gastrointestinal tolerability when compared to classical opioids. The dose of tapentadol does not have to be adjusted in the presence of renal impairment. Hepatoxicity has not been reported.

The incidence of nausea and vomiting has been seen to be lower in patients taking tapentadol as compared to patients taking oxycodone immediate release [44,60]. Tapentadol has been useful for postoperative pain after bunionectomy. Significant pain relief was obtained 32 to 46 minutes after surgery [61].

Tapentadol's two mechanisms of actions also may lend it opioid-sparing effects while maintaining adequate analgesia. Tapentadol is considered to have a potency between tramadol and morphine, with equivalent potency to that of opioids such as hydrocodone and oxycodone. The role of an oral preparation has inherent limitations in the acute postoperative period, but some recent data have shown its efficacy in dental surgery [62] and bunionectomy.

Tapentadol is contraindicated in patients with severe bronchial asthma, paralytic ileus, and in patients taking monoamine oxidase inhibitors (MAOI). Serotonin syndrome can develop with the use of tapentadol, and it should not be combined with serotonergic drugs such as selective serotonin reuptake inhibitor, selective norepinephrine reuptake inhibitor, tryptans, or tricyclic antidepressants, which can cause serotonin syndrome. Serotonin syndrome can include mental status changes such as hallucinations, coma, autonomic instability such as tachycardia, hyperthermia, and neuromuscular abnormalities such as hyperreflexia and incoordination.

ACUPUNCTURE FOR POSTOPERATIVE ANALGESIA

The term acupuncture describes a family of procedures involving the stimulation of anatomical points on the body using a variety of techniques. Acupuncture theory is based on two conditions: "yin," which is considered feminine, passive, dark, and cold, and "yang," which is masculine, aggressive, bright, and hot, as well as "qi," which is considered the vital energy that flows and cycles throughout the body. The acupuncture theory is to harmonize any imbalance in yin-yang and qi in a human body to restore the body to a healthy condition. Acupuncture is thought to unblock any obstruction to the flow of qi and, thereby, relieves pain. The acupuncture technique that has been most often studied scientifically involves penetrating the skin with thin, solid, metallic needles that are manipulated by the hands or electrical stimulation.

Acupuncture has been used to treat a variety of conditions such as chronic lower

back pain, chronic neck and shoulder pain, osteoarthritis of the knee, migraine headache, dysmenorrhea, labor pains, and acute post operative pain.

Sun et al. [63] conducted a systematic review to quantitatively evaluate the efficacy of acupuncture and related techniques as adjunct analgesics for acute postoperative pain management. The authors concluded that perioperative acupuncture might be a useful adjunct for acute postoperative pain management. However, there are issues with applicability and generalizability of the procedure [64].

Further, acupuncture is an umbrella term that encompasses several often disparate procedures. This can create confusion in scientific studies and their interpretation. To reduce this confusion, Usichenko et al. [65] focused on randomized controlled trials of only auricular acupuncture (a popular method in which needles are placed in various parts of the earlobe) for postoperative pain control. They identified nine studies of acceptable quality (though none of the best quality), of which eight upheld the superiority of auricular acupuncture over the control conditions. The mechanism of pain relief by auricular acupuncture is not known. The authors concluded that the evidence that auricular acupuncture controls postoperative pain is promising but not compelling. More research of methodologically rigorous design (especially ensuring therapist blindness, which none of the published studies addressed) on larger samples from different centers are needed to reach a definitive conclusion in this regard.

NEWER PATIENT-CONTROLLED ANALGESIC ROUTES

Patient-controlled regional analgesia

One of the most significant changes in surgical practice during the last two decades has been the growth of ambulatory surgery [66]. Adequate postoperative analgesia is a prerequisite for successful ambulatory surgery. Sending patients home with perineural, incisional, and intra-articular catheters is a new and evolving area of postoperative pain management. Current evidence suggests that these techniques are effective, feasible, and safe in the home environment if appropriate patient selection routines and organization for follow-up are in place [25,66].

Patient-controlled regional analgesia (PCRA) encompasses a variety of techniques that provide effective postoperative pain relief without systemic exposure to opioids [25]. Using PCRA, patients control the application of pre-programmed doses of local anesthetics, most frequently ropivacaine or bupivacaine (occasionally in combination with an opioid), via an indwelling catheter, which can be placed in different regions of the body depending upon the type of surgery. Infusions are controlled either by a staff-programmed electronic pump (similar to that used for IV PCA) or a disposable elastomeric pump. An elastomeric pump is a device that has a distensible bulb inside a protective bulb with a built-in filling port, delivery tube, and bacterial filter [56]. Analgesia can be delivered directly into a surgical incision (incisional PCRA), intra-articular (IA) tissue (IA PCRA), or perineural site (perineural PCRA).

Incisional PCRA

Placebo-controlled trials have established the efficacy and safety of incisional PCRA [67]. In an active-comparator trial [68], incisional PCRA with ropivacaine 0.5 percent via an elastomeric PCRA pump provided superior analgesia without major side effects compared with bolus infusion in patients recovering from arthroscopic subacromial decompression.

Intraarticular (IA) PCRA

Although IA administration of opioids with or without local anesthetics is established practice for joint anesthesia, studies evaluating IA PCRA are limited, as published data focus primarily on single-dose and continuous modes of IA administration. Vintar et al. [69] conducted a randomized, placebo-controlled trial evaluating the efficacy of ropivacaine/morphine (RM), ropivacaine/morphine/ketorolac (RMK), and saline

for postoperative pain management following anterior cruciate ligament construction. Patients self-initiated bolus doses of the analgesic mixture or saline solution via Microject PCA pump. While no significant differences in pain scores, side effects, and patient satisfaction were noted among the study groups, patients receiving RMK consumed significantly less rescue morphine per day compared with those receiving RM and placebo (RMK, 8 ± 8 mg; RM, 23 ± 20 mg; placebo, 46 ± 21 mg; $p < 0.001$).

Perineural PCRA

Perineural PCRA allows patients to self-titrate local anesthetic peripheral nerve blocks to achieve comfort. In a randomized, double-blind, placebo-controlled study (Ilfeld et al. [70]), perineural PCRA with ropivacaine 0.2 percent in the interscalene brachial plexus was shown to provide pain control superior to placebo in outpatients after moderately painful orthopedic surgery of the shoulder. On the first postoperative day, patients receiving perineural PCRA with ropivacaine reported significantly reduced pain ($P < 0.001$), less oral opioid use ($P < 0.001$), and lower sleep disturbance scores ($P = 0.13$) compared with patients receiving placebo infusions.

Rawal et al. [71] studied ambulatory patients receiving perineural PCRA into the brachial plexus at home. They have demonstrated that treatment with either ropivacaine 0.125 percent or bupivacaine 125 percent provides effective analgesia without signs and symptoms of local anesthetic toxicity. The incidence of side effects and technical problems was generally low with the most common complaint being numbness of the fingers (6.9 percent of ropivacaine patients and 29.0 percent of bupivacaine patients). On the day after surgery, the percentage of patients who were "satisfied or "very satisfied" was similar in the two groups (79 percent for ropivacaine and 83 percent for bupivacaine, respectively).

A number of studies have demonstrated that perineural PCRA results in equivalent or superior analgesic efficacy with lower total anesthetic consumption compared with continuous infusion in various settings and operations [72].

Patient-controlled intranasal analgesia (PCINA)

Intranasal (IN) opioids, either in the form of a dry powder or water or saline solution, are delivered using a syringe, nasal spray or dropper, or nebulized inhaler. In addition to needle-free administration, patient-controlled IN opioid administration (especially fentanyl) bypasses the hepatic first-pass effect and because of the excellent perfusion of the nasal mucosa, displays rapid absorption and rise in plasma concentration [73,74,75].

While evidence suggests that PCINA is efficacious, safe, noninvasive, and easy to administer, there have been only a limited number of small-sampled, randomized, placebo-controlled trials evaluating this route of analgesic administration in the postoperative period [75]. An acceptability study reported that 79 percent of patients receiving PCINA would want to use it again [76].

Patient-controlled transpulmonary analgesia

AeroLEF™ (aerosolized liposome-encapsulated Fentanyl; YM BioSciences Inc., Ontario, Canada) is a novel, proprietary inhalation formulation of free and liposome-encapsulated fentanyl intended to provide rapid, extended, and personalized analgesia for patients experiencing acute pain episodes. AeroLEF™ is in development for the treatment of moderate to severe pain, including cancer pain.

In contrast to fixed-dose approaches to opioid delivery, in which a significant titration period is often required to determine the suitable dose for the patient, AeroLEF™ is being developed to offer a simple and noninvasive route of administration, rapid onset of action, sustained effect, and self-titratable dosing for the treatment of acute and breakthrough pain. Using AeroLEF™, patients can identify and select a personalized dose for each pain episode, achieving both rapid onset and extended duration of analgesia. However, it is still a long way from being used in clinical practice.

ADVANCES IN ORGANIZATIONAL ASPECTS OF POSTOPERATIVE PAIN CONTROL

Procedure-specific analgesia

There is a need for the development of an evidence-based approach to reliable, comprehensive, individualized analgesic plans for specific surgical procedures. Although number-needed-to-treat (NNT) of a particular analgesic can give a valuable overview of efficacy, this concept is not necessarily applicable to all types of surgery. They proposed that procedure-specific acute pain management guidelines may be helpful because the pain intensity and its consequences may be procedure-related. Although the intensity of the acute pain state is expected to be related to the magnitude of the operation, this may not necessarily be so. When the size of the injury is considered, dental pain with a smaller injury may be relatively more painful compared with the pain observed in relation to the magnitude of tissue injury after hip replacement. However, the consequences of the injury and pain may be entirely different between these procedures because stress responses and organ dysfunctions resulting from the injury are different. The risk-benefit ratio of different analgesics also may vary according to the surgical procedure. Thus, the clinical effects of opioid sparing (which are variable between analgesics) also may depend on the effects of the surgical injury. Similarly, the risk and clinical implications of postoperative bleeding associated with certain analgesics are also procedure-specific. For example, the inhibition of platelet aggregation and, therefore, the risk of bleeding associated with NSAIDs are more relevant in operations that pose a risk of bleeding (e.g., a tonsillectomy). Therefore, analgesics with no effects on platelet function (e.g., acetaminophen and COX-2 specific inhibitors) may be preferable in these but not in other operations.

Kehlet et al. [77] argued that clinicians need information in which the choice of analgesic technique includes the consideration of the operation and is based on the available evidence from that particular surgical procedure. Such procedure specific guidelines are available from two sources: 1) the U.S. Veteran's Health Administration, in collaboration with the U.S. Department of Defense and the University of Iowa (www.oqp.med.va.gov/cpg/cpg.htm) [78], and 2) the PROSPECT Working Group (www.postoppain.org), a group of European anesthesiologists and surgeons [79].

CONCLUSION

With the many advances in pain management for the surgical patient, surgeons and pain care providers have myriad choices of analgesic pharmacotherapy and analgesic techniques to choose from to provide adequate postoperative pain control for the surgical patient in the 21st century. However, many factors must be considered before deciding on the type of pain therapy to be provided to the surgical patient. These include the patients' co-morbid conditions, psychological status, exposure to analgesic therapies, and the type of surgical procedure.

In the future, genetically informed "personalized medicine" may become a reality even for acute pain management. With the recent advent of studies documenting genetic polymorphisms with respect to pain response to morphine [80] and pressure pain sensitivity [81], this exciting possibility looks promising in the near future.

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