Preventing the Development of Chronic Pain After Orthopaedic Surgery with Preventive Multimodal Analgesic Techniques

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Current Concepts Review

Preventing the Development of Chronic Pain After Orthopaedic Surgery with Preventive Multimodal Analgesic Techniques

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- The prevalences of complex regional pain syndrome, phantom limb pain, chronic donor-site pain, and persistent pain following total joint arthroplasty are alarmingly high.
- Central nervous system plasticity that occurs in response to tissue injury may contribute to the development of persistent postoperative pain. Many researchers have focused on methods to prevent central neuroplastic changes from occurring through the utilization of preemptive or preventive multimodal analgesic techniques.
- Multimodal analgesia allows a reduction in the doses of individual drugs for postoperative pain and thus a lower prevalence of opioid-related adverse events. The rationale for this strategy is the achievement of sufficient analgesia due to the additive effects of, or the synergistic effects between, different analgesics.
- Effective multimodal analgesic techniques include the use of nonsteroidal anti-inflammatory drugs, local anesthetics, α-2 agonists, ketamine, α_2-δ ligands, and opioids.

One of the potential complications following an operation is the development of chronic pain. The prevalence of persistent postoperative pain (for more than three to six months) remains alarmingly high, and such pain has been reported after numerous operative procedures including limb amputation, thoracotomy, mastectomy, cholecystectomy, and surgery for an inguinal hernia[1,2]. Clearly there is substantial variability in the prevalence of chronic pain following each of these procedures, and specific risk factors for its development have been identified. These factors include, among others, preoperative pain of more than one month in duration, the intensity of acute postoperative pain, psychological vulnerability and anxiety, and an operative approach that involves the possibility of nerve damage[1]. Furthermore, recent research has revealed that genetic factors may play a role in the development of chronic pain. Sensitivity to physiological nociceptive and clinical pain differs considerably among individuals. Increasingly, this inconsistency is recognized as an indication of differential heritable susceptibility both to the generation and experience of pain and to the response to analgesics[3]. For example, functional genetic polymorphisms of catecholamine-O-methyltransferase (COMT) are associated with altered sensitivity to pain induced in an experimental environment[3] . High COMT activity correlates with the risk of chronic temporomandibular joint pain developing[3].

Despite the identification of chronic postoperative pain syndromes, little is known about the underlying mechanisms, natural history, and response to therapy of each syndrome[4]. It is now recognized that nociceptor function is dynamic and may be altered following tissue injury, which may contribute to persistent pain[5,6]. The perception of pain is not a predictable neurophysiological mechanism wherein stimuli are always transmitted and processed in an identical manner. In fact, the central nervous system exhibits a great deal of plasticity. The processing of pain signals is now recognized to be a complex physiological cascade that involves dozens of different neurotransmitters and chemical substrates at several different anatomical locations.

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Operative procedures produce an initial afferent barrage of pain signals and generate a secondary inflammatory response, both of which contribute substantially to postoperative pain. The signals have the capacity to initiate prolonged changes in both the peripheral and the central nervous system that lead to the amplification and prolongation of postoperative pain. Peripheral sensitization, a reduction in the threshold of nociceptor afferent peripheral terminals, is a result of inflammation at the site of surgical trauma[5]. Central sensitization, an activity-dependent increase in the excitability of spinal neurons, is a result of persistent exposure to nociceptive afferent input from the peripheral neurons[5] (Fig. 1). Taken together, these two processes contribute to the postoperative hypersensitivity state (the so-called spinal wind-up) that is responsible for a decrease in the pain threshold, both at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia) (Fig. 1). This is the mechanism by which pain may be prolonged beyond the duration normally expected following an acute insult. Prolonged central sensitization has the capacity to lead to permanent alterations in the central nervous system, including the death of inhibitory neurons, replacement with new afferent excitatory neurons, and establishment of aberrant excitatory synaptic connections[6]. These alterations lead to a prolonged state of sensitization, resulting in intractable postoperative pain that is unresponsive to many analgesics[7].

As evidence concerning the role of sensitization in the prolongation of postoperative pain continues to accumulate, many researchers have focused on methods that do not simply treat symptoms as they occur but rather prevent wind-up from occurring. The evidence in support of these preemptive analgesic techniques has been equivocal: one systematic review of the literature demonstrated no beneficial effect[8], whereas a more recent review[9] demonstrated an overall benefit. However, the concept of preemptive analgesia has evolved beyond the importance of reducing the nociceptive afferent input brought about by the surgical incision. The term *preventive analgesia*[10] was introduced to emphasize the fact that central neuroplasticity is induced by preoperative, intraoperative, and postoperative nociceptive inputs. Thus, the goal of preventive analgesia is to reduce the central sensitization that arises from noxious inputs experienced throughout the entire perioperative period and not just from those occurring during the surgical incision. Preemptive treatment should be directed at the periphery, along the sensory axons, and along the central neurons. This can be accomplished with the use of nonsteroidal anti-inflammatory drugs, acetaminophen, local anesthetics, α-2 agonists (e.g., clonidine), α_2-δ ligands (e.g., gabapentin and pregabalin), ketamine, and opioids, either alone or in combination (Fig. 2). It is important to administer these analgesics at the doses outlined in Table I, both prior to the surgical incision and postoperatively before the develop-

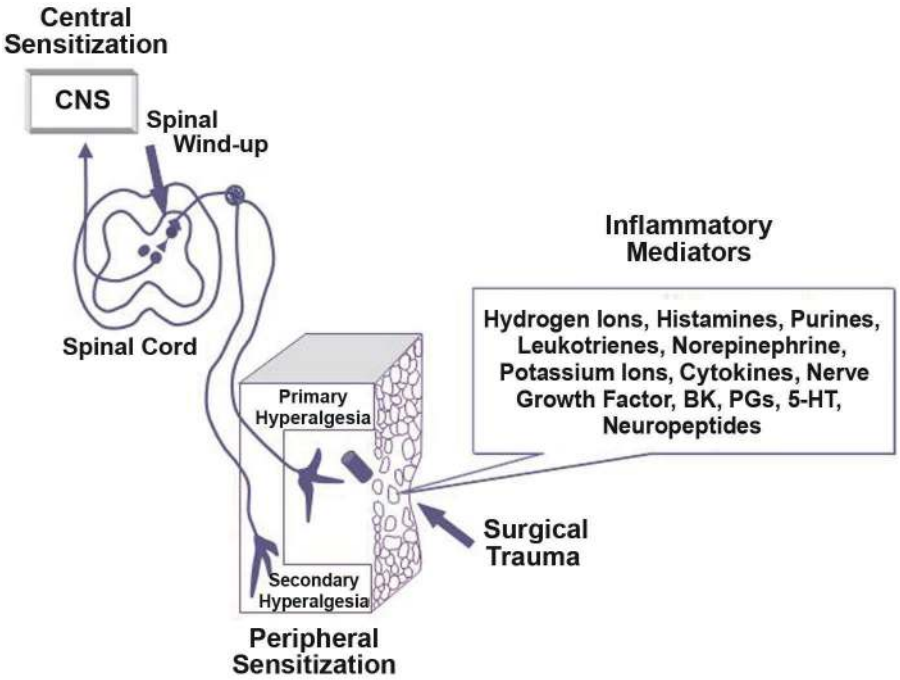

Fig. 1

Surgical trauma leads to the release of inflammatory mediators at the site of injury, resulting in a reduction in the pain threshold at the site (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia). Peripheral sensitization results from a reduction in the threshold of nociceptor afferent terminals secondary to surgical trauma. Central sensitization is an activity-dependent increase in the excitability of spinal neurons (spinal wind-up) as a result of persistent exposure to afferent input from peripheral neurons. CNS = central nervous system, BK = bradykinin, PGs = prostaglandins, and 5-HT = serotonin.

TABLE I Multimodal Analgesics

Analgesic	Preoperative Dose	Maintenance Dose
Acetaminophen	1000 mg orally	1000 mg every 6 h
Celecoxib	400 mg orally	200 mg every 12 h
Ketamine	20-70 mg intravenously	20-30 mg every 1 h
Gabapentin	600-1200 mg orally	300-600 mg every 8 h
Pregabalin	150 mg orally	75-150 mg every 12 h
Morphine		
Epidural	1-3 mg	Not applicable
Intrathecal	0.1-0.3 mg	Not applicable
Intra-articular	3-5 mg	Not applicable
Intrawound	3-5 mg	Not applicable
Clonidine		
Epidural	100-200 μg	1-10 μg every 1 h
Intrathecal	10-50 μg	Not applicable
Intra-articular	70-100 μg	Not applicable
Intravenous regional anesthesia	70-100 μg	Not applicable
Peripheral nerve block	70-100 μg	Not applicable

ment of severe pain. Effective preventive analgesic techniques may be useful not only for reducing acute pain but also for reducing chronic postoperative pain and disability.

In this review, we examine the efficacy of a variety of multimodal analgesic techniques and review the evidence regarding whether these analgesics may be administered preemptively to reduce chronic pain following an operation. Four chronic postoperative pain syndromes that are important clinically to orthopaedic surgeons are complex regional pain syndrome, phantom limb pain, chronic donor-site pain, and persistent pain following total joint arthroplasty.

Multimodal Analgesia

Opioids are still considered to play a major role in the management of pain following orthopaedic surgery, although they may contribute to increased hospital morbidity and health-care costs[11]. Adverse events associated with the use of opioids in the postoperative setting include nausea and vomiting, respiratory depression, sedation, pruritus, urinary retention, and sleep disturbances[12]. In July 2000, the Joint Commission on Accreditation of Healthcare Organizations introduced a new standard for pain management, declaring the pain level to be the "fifth vital sign."[13] The Commission concluded that acute and chronic pain are major causes of patient dissatisfaction in the United States health-care system, leading to slower recovery times, creating a burden for patients and their families, and increasing costs. However, reducing postoperative pain with opioids alone will increase the risk of adverse effects[14-16].

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the prevalence of opioid-related adverse events[17]. The rationale for this strategy is the achievement of sufficient analgesia due to the additive or synergistic effects of different analgesics. This allows a reduction in the doses of these drugs and thus a lower prevalence of adverse effects. Unfortunately, unimodal pain treatment was used in most of the studies on acute pain management in the literature. Such treatment cannot be expected to provide sufficient pain relief to allow normal function without the risk of adverse effects[17,18]. Most of the literature about pain fails to address the issue of pain during daily function (such as coughing, walking, and physical therapy). It has been demonstrated that, in addition to lowering the prevalence of adverse effects and improving analgesia, multimodal analgesia techniques may shorten hospitalization times, improve recovery and function, and decrease health-care costs following orthopaedic surgery[19-21]. Currently, the Agency for Healthcare Research and Quality[22] and the American Society of Anesthesiologists Task Force on Acute Pain Management[23] advocate the use of multimodal analgesia. As described in the literature, multimodal analgesic regimens for orthopaedic surgery include local anesthetics, α-2 agonists (e.g., clonidine), nonsteroidal anti-inflammatory drugs, acetaminophen, ketamine, α_2-δ ligands (e.g., gabapentin and pregabalin), and opioids (Fig. 2).

Clonidine and Other α-2 Agonists

Experimental research on animals supports the contention that α-2 adrenergic agonists have analgesic actions at the peripheral, spinal, and brainstem sites. This is evidenced by the detection of α-2 adrenoceptors on primary afferent terminals, on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei[24]. The precise mechanism by which clonidine exerts its analgesic effect remains unknown. Clonidine enhances peripheral nerve blocks with local anesthetics by selectively blocking conduction of A-δ and C

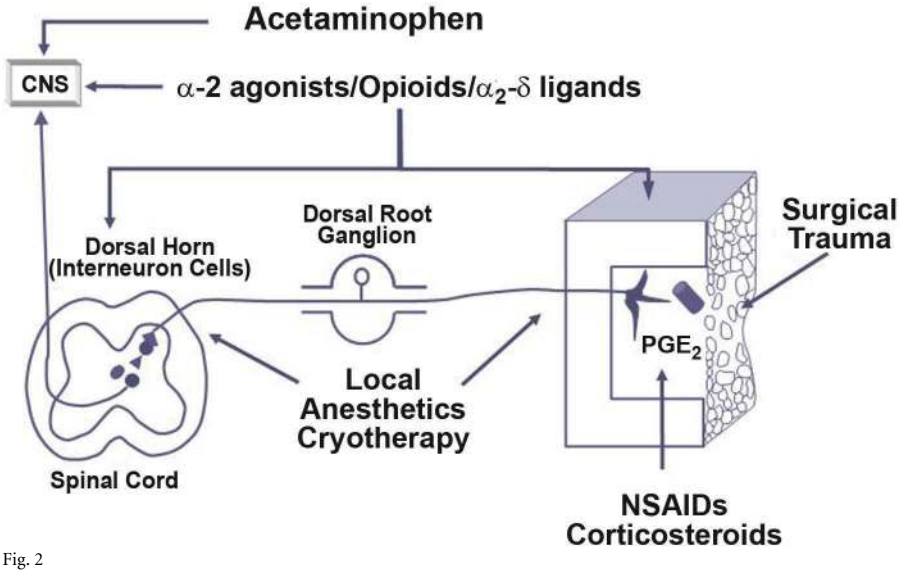

Fig. 2

Drawing depicting the sites of action of analgesics along the pain pathway from the periphery to the central nervous system (CNS). NSAIDs = nonsteroidal anti-inflammatory drugs, and PGE_2 = prostaglandin E_2.

fibers[25-27]. Clonidine also causes local vasoconstriction, thereby reducing the vascular uptake of local anesthetics[28], although this mechanism is controversial[29]. Recent animal studies in which clonidine was used for peripheral nerve blocks have suggested that the mechanism of action is mediated by the hyperpolarization-activated cation current (Ih) and not by the α-2-adrenoceptors[30]. Clonidine may also produce an analgesic effect by releasing enkephalin-like substances[31]. In addition, because sympathetic neural activity might increase both somatic[32] and sympathetically maintained pain[33], clonidine can reduce nociceptive pathways by inhibiting the release of norepinephrine from prejunctional α-2 adrenoceptors. Only recently has clonidine been available in the United States as a parenteral preparation (Duraclon; Roxane Laboratories, Columbus, Ohio). This has led to a multitude of studies focusing on the analgesic efficacy of administering clonidine as a regional analgesic block in the management of both acute and chronic pain[34].

A central neuraxial block with a local anesthetic and clonidine improves the quality of analgesia after total joint arthroplasty[35-39]. The combination of intrathecal clonidine and morphine provided analgesia that was superior to that provided by intrathecal morphine alone following total knee arthroplasty[35]. Administration of clonidine with an epidural infusion of a local anesthetic and fentanyl improved analgesia and reduced the need for rescue opioid medication following total knee arthroplasty[36]. Continuous long-term (thirty to forty-day) epidural infusions of clonidine, bupivacaine, and fentanyl through a tunneled epidural catheter improved the range of motion in patients who underwent total knee arthroplasty and had been identified preoperatively as having risk factors for the development of chronic pain[37]. Clonidine also improved postoperative analgesia when it was added to epidural infusions of a local anesthetic[38] or during combined spinal-epidural anesthesia for total hip arthroplasty[39].

Clonidine has also been shown to enhance peripheral nerve blocks when added to a variety of local anesthetics[34]. The addition of clonidine (1 μg/kg) to 0.5% lidocaine for intravenous regional anesthesia was found to improve postoperative analgesia during the first day after hand surgery, with no apparent adverse effects[40]. Also, the use of clonidine for intravenous regional anesthesia was shown to allow longer tourniquet-inflation times before the onset of intolerable pain in healthy, unsedated volunteers[41]. In addition to nociceptive pain, sympathetically mediated pain has also been shown to be treated effectively with intravenous regional anesthesia with clonidine[42,43]. The analgesic effect of intravenous regional anesthesia with clonidine appears to be peripherally mediated and not due to central redistribution, as the same dose administered parenterally provided no additional analgesia[40]. Furthermore, the concentration of clonidine in plasma (0.12 ng/mL) measured after tourniquet deflation[42] was considerably lower than the concentration required for a central analgesic effect (1.5 to 2 ng/mL) when clonidine is administered through the parenteral route to manage postoperative pain[44].

In addition to being beneficial when it is administered with local anesthetics, clonidine possesses an analgesic efficacy when it is administered by itself through the intra-articular route[45]. Furthermore, the addition of intra-articular clonidine to morphine and bupivacaine enhanced the analgesic efficacy of both drugs[46]. The peripheral administration of clonidine is a useful nonopioid analgesic technique that currently plays an important role in the management of both acute and chronic pain related to orthopaedic surgery.

Nonsteroidal Anti-Inflammatory Drugs and Acetaminophen

It has become apparent that the products of arachidonic metabolism promote the pain and hyperalgesia associated with tissue trauma and inflammation (Fig. 3). Under normal conditions, tissues possess a cell membrane that is composed of a bipolar lipoprotein configuration with phospholipids sequestered within the membrane. Following tissue injury, the cell membrane is disrupted and the previously inaccessible phospholipids are exposed to the enzyme phospholipase A_2 in the periphery, which catalyzes the conversion to arachidonic acid (Fig. 3). Arachidonic acid in turn acts as a substrate for the cyclooxygenase (COX)-2 enzyme, which produces the short-lived prostaglandins (PG) including PGG_2 and PGH_2. Several synthases then convert PGH_2 to other prostaglandins (e.g., PGD_2, PGE_2, PGF_2-alpha, and PGI_2) and to thromboxane A_2. These prostaglandins do not generally activate nociceptors directly but sensitize them to mechanical stimuli and chemical mediators of nociception, resulting in hyperalgesia and thus facilitating pain transmission[47]. PGE_2 is the predominant prostanoid associated with inflammatory responses and is responsible for reducing the pain threshold at the site of injury (primary hyperalgesia), resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue (secondary hyperalgesia)[48]. Nonsteroidal anti-inflammatory drugs are thought to reduce postoperative pain by suppressing COX-2-mediated production of PGE_2.

The primary site of action of nonsteroidal anti-inflammatory drugs is believed to be in the periphery, although recent research indicates that central inhibition of COX-2 may also play an important role in modulating nociception[49].

Nonsteroidal anti-inflammatory drugs inhibit the synthesis of prostaglandins both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after surgical trauma[49]. Nonsteroidal anti-inflammatory drugs are useful as the sole analgesic after minor operative procedures[50], and they may have an important opioid-sparing effect after a major operation[51]. The use of these drugs has become increasingly popular because of the concern about opioid-related side effects. All nonsteroidal anti-inflammatory drugs have a ceiling effect for analgesia, but they do not demonstrate a ceiling effect with regard to side effects[52]. The recent practice guidelines for acute pain management in the perioperative setting specifically state: "Unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COXIBs, or acetaminophen."[23]

Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties similar to those of aspirin. The mechanism of action of acetaminophen is still poorly defined. Recent evidence has suggested that it may selectively act as an inhibitor of prostaglandin synthesis in the central nervous system rather than in the periphery[53]. The theory that acetaminophen acts through the COX-3 receptor[54] has recently been challenged[55]. In addition, there is evidence that serotonergic mechanisms are involved in the antinociceptive activity of acetaminophen[56]. A meta-analysis of randomized controlled trials of the use of acetaminophen for postoperative pain revealed that this analgesic induced a morphine-sparing

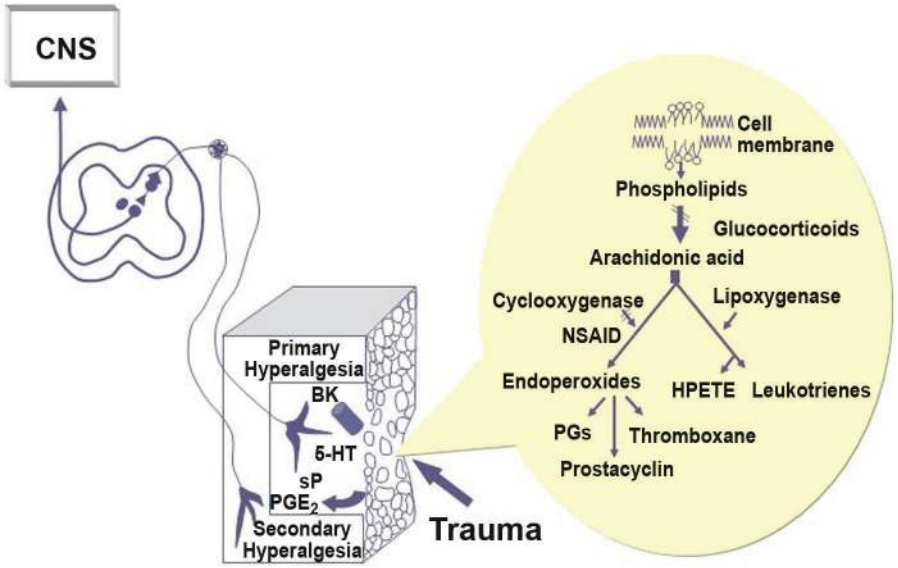

Fig. 3

Tissue injury results in the release of a variety of nociceptive agonists including bradykinin (BK), serotonin (5-HT), substance P (sP), and arachidonic acid cascade metabolites. Arachidonic acid can be metabolized to either the prostaglandin endoperoxides, including prostaglandin E_2 (PGE_2), by the cyclo-oxygenase enzyme or to hydroperoxyeicosatetraenoic acid (HPETE) and leukotrienes by the lipo-oxygenase pathway. Prostaglandins, including PGE_2, are responsible for reducing the pain threshold at the site of injury (primary hyperalgesia), resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue (secondary hyperalgesia). CNS = central nervous system.

effect of 20% over the first twenty-four hours postoperatively but did not reduce the prevalence of morphine-related adverse effects[57]. The authors of a recent qualitative review of acetaminophen, nonsteroidal anti-inflammatory drugs, and their combination concluded that acetaminophen may provide analgesic efficacy similar to that of other nonsteroidal anti-inflammatory drugs following major orthopaedic surgery[58]. It was thought that acetaminophen may be a viable alternative to nonsteroidal anti-inflammatory drugs in high-risk patients because of the lower prevalence of adverse effects[58]. Furthermore, it may be appropriate to administer acetaminophen with nonsteroidal anti-inflammatory drugs or COX-2 inhibitors since these two analgesics may act additively or synergistically to improve analgesia[59].

A recent meta-analysis was done to examine whether there is any advantage to adding acetaminophen, nonsteroidal anti-inflammatory drugs, or COX-2 inhibitors to patient-controlled analgesia with morphine[60]. The results suggested that all of the analgesic agents provided an opioid-sparing effect but this decrease in morphine intake did not consistently result in a decrease in opioid-related adverse effects. The use of nonsteroidal anti-inflammatory drugs was associated with a decrease in the prevalence of postoperative nausea and vomiting and sedation. However, the use of COX-2 inhibitors or acetaminophen did not decrease the prevalence of opioid-related adverse events when compared with those associated with a placebo.

A systematic review comparing COX-2 inhibitors with traditional nonsteroidal anti-inflammatory drugs for management of postoperative pain showed that these two analgesics demonstrate equipotent analgesic efficacy after minor and major operative procedures[61]. Since COX-2 inhibitors are associated with reduced gastrointestinal side effects and an absence of anti-platelet activity, they can be administered to patients treated with orthopaedic surgery without the added risk of increased perioperative bleeding that has been reported with conventional nonsteroidal anti-inflammatory drugs[59]. Recent studies have demonstrated improved analgesia, shorter hospitalization times, improved recovery and function, and decreased health-care costs with the use of COX-2 inhibitors in the multimodal management of pain following orthopaedic surgery[19-21].

One potential concern regarding the use of COX-2 inhibitors has been their possible role in increasing cardiovascular morbidity[62]. Theoretical concerns were borne out when a fivefold increase in the prevalence of myocardial infarction was seen in the Vioxx Gastrointestinal Outcome Research (VIGOR) study[63]. Several clinicians attributed the increase in adverse cardiovascular events to a prothrombotic state caused by selective COX-2 inhibitors[64]. Valdecoxib and the parenteral prodrug parecoxib have also been associated with an increased risk of myocardial infarctions (1.6% compared with 0.7% in a control group) after administration of a supramaximal dose (40 mg twice daily) for fourteen days following coronary artery bypass grafting[65]. However, no increase in cardiovascular events was observed after administration of a therapeutic dose of parecoxib followed by a therapeutic dose of valdecoxib for patients treated with general and orthopaedic procedures[66].

On the basis of a review of data on users of nonsteroidal anti-inflammatory drugs enrolled in the Kaiser Permanente health-care system in California, it became apparent that cardiovascular toxicity may be related to all nonsteroidal anti-inflammatory drugs and not just COX-2-specific inhibitors[67]. During 2,302,029 person-years of follow-up, this study showed a significantly increased risk of adverse cardiovascular events among users of diclofenac (relative risk = 1.69; $p = 0.06$), indomethacin (relative risk = 1.30; $p = 0.005$), and naproxen (relative risk = 1.14; $p = 0.01$) compared with that among individuals who did not use nonsteroidal anti-inflammatory drugs. A joint meeting of the United States Food and Drug Administration (FDA) Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee in 2005 reaffirmed that COX-2 inhibitors are important treatment options for pain management and that the cardiovascular risk associated with celecoxib is similar to that associated with commonly used nonspecific nonsteroidal anti-inflammatory drugs[68]. The FDA announced a series of changes applicable to the entire class of nonsteroidal anti-inflammatory drugs[68]. These included an FDA "black box" warning about the potentially increased risk of cardiovascular events and gastrointestinal bleeding associated with all prescription nonsteroidal anti-inflammatory drugs, including celecoxib. The FDA noted that all nonsteroidal anti-inflammatory drugs can lead to the onset of new hypertension or worsening of preexisting disease, either of which may contribute to an increased prevalence of cardiovascular events. Therefore, nonsteroidal anti-inflammatory drugs and coxibs that are to be used to manage pain should be prescribed at the lowest effective dose for the shortest duration. They should not be prescribed for high-risk patients (e.g., those with a history of ischemic heart disease, stroke, or congestive heart failure or those who have recently undergone coronary artery bypass grafting).

With the withdrawal of rofecoxib and valdecoxib from the worldwide market, celecoxib is currently the only COX-2 nonsteroidal anti-inflammatory drug approved for the management of pain in the United States. Parecoxib (an injectable prodrug of valdecoxib), etoricoxib, and lumaricoxib are currently available in Latin America and Europe.

Ketamine

Ketamine has been a well-known general anesthetic and analgesic for the past three decades. With the discovery of the N-methyl-D-aspartate (NMDA) receptor[69] and its links to nociceptive pain transmission and central sensitization[70], there has been renewed interest in utilizing ketamine as a potential antihyperalgesic agent given its actions as a noncompetitive NMDA receptor antagonist[70]. Although high doses (>2 mg/kg) of ketamine have been implicated in causing psychomimetic effects (excessive sedation, cognitive dysfunction, hallucinations, and nightmares), subanesthetic or low doses (<1 mg/kg) of ketamine have demonstrated substantial analgesic efficacy without these side effects[71,72]. Furthermore, there is no evidence

that low-dose ketamine exerts any adverse pharmacological effect on respiratory, cardiovascular, or gastrointestinal function[71]. Authors of recent systematic reviews have concluded that intravenous, intramuscular, or subcutaneous administration of low-dose ketamine as the sole analgesic agent reduces pain[71,72]. In contrast, there is little evidence to support the use of low-dose epidural ketamine by itself for postoperative analgesia[71]. There is a growing body of evidence that low-dose ketamine may play an important role in improving postoperative pain management when used as an adjunct to opioids or local anesthetics[71,72]. However, despite the opioid-sparing effect observed with the administration of ketamine, to our knowledge no reduction in opioid-related side effects has been documented[71,72]. Ketamine may also be useful when added to local anesthetic solutions for wound infiltration, resulting in improved analgesia that is mediated by means of a peripheral mechanism[73]. Ketamine is being used more frequently in the management of pain following orthopaedic surgery. A single intraoperative injection of ketamine (0.15 mg/kg) improved analgesia and passive knee mobilization twenty-four hours after arthroscopic anterior cruciate ligament surgery[74] and improved the postoperative functional outcome after outpatient knee arthroscopy[75]. Low-dose ketamine can also increase pain relief after total knee arthroplasty when it is used in conjunction with either epidural anesthesia[76] or a continuous femoral nerve block[77]. Patients who had received perioperative ketamine also had an earlier improvement in knee function following total knee arthroplasty[77].

Local Anesthetics and Regional Analgesia

The use of regional anesthetic techniques for the perioperative management of pain is not a new concept. Crile believed that, compared with general anesthesia alone, a combination of local regional blocks and general anesthesia improved analgesia and enhanced postoperative convalescence, especially when the blocks had been performed in advance of the painful stimulus[78]. In 1913, he concluded that "patients given inhalational anesthesia still need to be protected by regional anesthesia otherwise they might incur persistent central nervous system changes and enhanced postoperative pain."[78]

Wound Infiltration

Infiltrating local anesthetics into the skin and subcutaneous tissues prior to making an incision may be the simplest approach to preemptive analgesia. It is a safe procedure with few side effects and a low risk of toxicity. Although the benefit of local wound infiltration has been documented, there is controversy regarding the appropriate timing of administration of local anesthesia for surgery. In a meta-analysis of fourteen randomized trials (736 patients) comparing pre-incisional with post-incisional wound infiltration for a variety of surgical procedures (including orthopaedic surgery), Moiniche et al.[8] found no difference in analgesic efficacy between the two techniques. In contrast, in a review of fifteen randomized trials (671 patients), Ong et al.[9] concluded that preemptive local infiltration reduced analgesic consumption and the time to the patient's first request for analgesia but did not reduce pain intensity when compared with post-incisional infiltration. It remains unclear from these data whether local anesthetic infiltration into the wound prevents chronic incisional pain over the long term. Most of the authors of these studies terminated their assessment of the effect at twenty-four to forty-eight hours, well before the abatement of the acute postoperative pain.

With the recent technologic improvements in nonelectric disposable infusion pumps[79], techniques for continuous infusion of local anesthetics are increasing in popularity for orthopaedic operations performed both in the hospital and on an outpatient basis[80]. Continuous infusions of bupivacaine either intra-articularly[81] or into the infrapatellar fat pad[82] have demonstrated analgesic efficacy for patients undergoing anterior cruciate ligament reconstruction. The effectiveness of anesthetic continuous-infusion devices was also demonstrated for patients treated with outpatient shoulder surgery in a randomized, double-blind trial[83]. That trial revealed that a continuous infusion of bupivacaine for forty-eight hours after surgery reduced pain and opioid use both during use of the pump and for several days after its use was discontinued. The infusion of bupivacaine either into the wound or as a local nerve block has also proven to be an effective analgesic technique for the management of pain following hand surgery[84] and following harvest of iliac crest bone graft[85]. However, the continuous infusion of bupivacaine has not demonstrated efficacy for the management of pain following total knee arthroplasty[86]. It was concluded that drug loss from the knee drainage may exceed 25% of the intra-articular infusion, compromising the analgesic effectiveness of this technique for total knee arthroplasty[86].

Other concerns about local anesthetic-infusion techniques include the possibility of infection and chondrotoxicity. In a study of the efficacy of continuous infusions of bupivacaine for patients treated with hand surgery, investigators reported that an infection developed at the cannula insertion site in two of 100 subjects after one week[84]. Furthermore, a recent animal study showed that infusion of bupivacaine for forty-eight hours led to profound histopathologic and metabolic changes in articular cartilage[87]. The authors of that study cautioned against the use of continuous infusion devices in smaller joints. Future large-scale studies of humans are needed to address the efficacy and safety (with regard to chondrotoxicity and localized infection) of infusion pumps before this technique becomes widely used to manage pain after orthopaedic surgery.

Peripheral Nerve Blocks

Peripheral nerve blocks are an attractive method of providing postoperative analgesia for many orthopaedic surgical procedures. When compared with general anesthesia, these blocks have been associated with superior same-day recovery and decreases in hospital readmissions[80]. Although single-injection regional anesthesia is effective for early analgesia, it does not provide a long-term benefit compared with general anesthe-

sia[88]. A recent meta-analysis revealed that, compared with opioid analgesia alone, use of continuous peripheral nerve blocks following orthopaedic surgery provides superior analgesia and reduces opioid use and opioid-related side effects[89]. Currently, there is insufficient evidence to determine the effectiveness of continuous peripheral analgesic techniques on long-term functional outcomes[90].

Epidural Blocks

In addition to providing subjective comfort, physicians need to inhibit trauma-induced afferent pain transmission and to blunt the autonomic and somatic reflex responses to pain following orthopaedic surgery. The neuroendocrine stress response that follows surgery has the capacity to induce important disturbances in body homeostasis such as hypercatabolism, hypercoagulability, and inflammation, which can contribute to adverse perioperative outcomes[91]. Parenteral opioids do not reduce this stress response adequately following orthopaedic surgery[92], and they provide inferior analgesia when compared with epidural techniques for the management of postoperative pain[93]. Epidural analgesia is superior to either peripheral nerve blocks or patient-controlled analgesia for blunting the stress response following orthopaedic surgery[92]. The question facing orthopaedic surgeons is whether blocking the neuroendocrine stress response improves patient outcomes. Meta-analyses of hip fracture repairs[94] and total hip arthroplasties[95] showed that neuraxial block (spinal or epidural) anesthesia decreased the prevalences of deep venous thrombosis and pulmonary embolism, intraoperative blood loss, and blood transfusion requirements but had no effect on the one-year mortality rate. In two other clinical investigations, early administration of continuous epidural analgesia during the stressful preoperative period was associated with a lower prevalence of adverse cardiac events[96,97], compared with that associated with conventional analgesia, in high-risk patients with a hip fracture.

Unfortunately, epidural anesthesia and analgesia are contraindicated for patients receiving anticoagulation therapy. For this reason, many institutions are utilizing alternative regional analgesic techniques for orthopaedic surgery. A prospective randomized study was performed to evaluate the effect of continuous epidural anesthesia, a continuous femoral nerve block, or intravenous patient-controlled analgesia maintained for seventy-two hours following total knee arthroplasty[98]. The first two techniques were performed with use of multimodal analgesics including lidocaine, clonidine, and morphine. Compared with intravenous patient-controlled analgesia, both regional techniques provided superior analgesia, reduced the duration of the rehabilitation stay, and improved functional outcomes. Because the prevalence of side effects associated with a continuous femoral block was lower than that associated with epidural analgesia and because the block does not cause neuraxial hematoma, the authors concluded that this technique has all of the qualities necessary to become the primary choice for regional analgesia after total knee arthroplasty[98].

Opioids (Peripheral and Central Acting)

Opioids possess analgesic properties through action on opioid receptors located in the central nervous system. The preoperative administration of opioids may attenuate the central hyperexcitability response that occurs as a result of surgical trauma[99]. Several clinical investigations have shown preoperative administration of opioids to be an effective analgesic technique for the management of postoperative pain[100-103]. McQuay et al.[102] demonstrated a prolonged duration of analgesia and a reduction in the use of postoperative analgesics when opiates had been administered to patients before they underwent elective orthopaedic surgery. Preoperative opioids have demonstrated efficacy when utilized as a component of a multimodal analgesic regimen for patients undergoing minimally invasive joint-replacement surgery[103].

One concern regarding the perioperative use of opioids is the development of opioid-induced hyperalgesia[104,105]. During the last decade, there has been accumulating evidence that, in addition to the enhanced pain sensitivity found with the long-term administration of opioids, both hyperalgesia and allodynia can occur after the short-term use of opioids following abdominal and orthopaedic procedures[104,105]. Furthermore, the larger the intraoperative opioid dose, the greater the postoperative opioid requirement[106]. Therefore, short-term tolerance to an opioid may not be due to a decrease in its efficacy (pharmacological tolerance) but rather may be due to enhancement of pain sensitivity (opioid-induced hyperalgesia) leading to an apparent decrease in the effectiveness of the morphine[104,105]. The use of multimodal adjuvant drugs for postoperative pain may reduce opioid-induced hyperalgesia. Experimental and clinical studies have suggested that opioids activate both NMDA[107] and COX[108] pro-nociceptive systems leading to hyperalgesia. Therefore, the use of the NMDA receptor antagonists (ketamine) and nonsteroidal anti-inflammatory drugs not only decreases postoperative pain but may also reduce opioid-induced tolerance and hyperalgesia[107,108].

In addition to the central action of opioids, recent studies have revealed that, under conditions of inflammation, these analgesics can produce substantial antinociception through peripheral mechanisms[109]. This has led to a growing number of clinical studies of the analgesic efficacy of opioids applied locally through the intra-articular, perineural, or intravenous regional route[110,111]. The most consistent clinical results concerning the analgesic efficacy of peripherally applied opioids in humans have come from studies involving the intra-articular administration of morphine during arthroscopic knee surgery[111,112]. Similar to the parenteral route[99], the preemptive peripheral administration of morphine can also reduce postoperative pain[113]. Although the majority of investigators[112] have examined the analgesic efficacy of administering intra-articular morphine at the conclusion of an operation, two groups of authors[114,115] concluded that preoperative intra-articular administration of morphine is a more effective technique for managing pain following arthroscopic knee surgery. Because only small, systemically inactive doses of opioids are required to provide sustained analgesia with minimal side effects, intra-

articular administration is an important technique in the management of pain following orthopaedic surgery.

Gabapentin and Pregabalin (α_2-δ Ligands)

Both gabapentin and pregabalin are alkylated χ-aminobutyric acid analogs that were first developed clinically as anticonvulsants. These drugs bind to the α_2-δ subunit of voltage-gated calcium channels, thus preventing release of nociceptive neurotransmitters including glutamate, substance P, and noradrenaline[116]. Putative sites of action include peripheral, primary afferent neuron, spinal neuron, and supraspinal sites[117]. These anticonvulsants can enhance the analgesic effect of morphine[118], nonsteroidal anti-inflammatory drugs[119], and COX-2 inhibitors[120]. Recent evidence suggests that, in addition to being effective analgesics for patients with neuropathic or chronic pain syndromes, these anticonvulsants provide effective postoperative analgesia when they are administered preemptively before an operation[121,122]. The role of certain neural changes common to both neuropathic and postoperative pain may explain these recent observations[48,101]. Perioperative administration of gabapentin has been found to be efficacious for managing pain following various orthopaedic surgical procedures, including anterior cruciate ligament and spinal operations[121,122]. A single preoperative 1200-mg dose of gabapentin was shown to reduce preoperative anxiety as well as postoperative pain scores and opioid use and to improve the range of motion for up to forty-eight hours following anterior cruciate ligament surgery[123]. Furthermore, since these drugs can interact synergistically with nonsteroidal anti-inflammatory drugs to produce antihyperalgesia[121,122], the use of nonsteroidal anti-inflammatory drugs and α_2-δ ligands together may provide more effective analgesia. The combination of pregabalin and celecoxib was recently shown to be superior to either single agent alone for management of pain following spinal fusion surgery[124]. This was evidenced by a significant ($p < 0.001$) reduction in pain scores and morphine use and fewer side effects during the first twenty-four postoperative hours in patients treated perioperatively with celecoxib and pregabalin.

The most commonly observed adverse events associated with the long-term use of gabapentin and pregabalin are dizziness, somnolence, and peripheral edema[125]. A meta-analysis indicated that perioperative treatment with gabapentin was associated with only a modest increase in sedation[122]. Although sedation can be interpreted as a negative outcome of gabapentin use, its occurrence in the perioperative setting may be beneficial in terms of contributing to anxiolysis[123]. Future studies are necessary to determine the optimal timing, duration, dosages, and impact on chronic persistent pain of administration of α_2-δ ligands in association with a variety of orthopaedic surgical procedures.

Overview on Multimodal Analgesia

In summary, although these analgesic adjuvant medications (local anesthetics, α-2 agonists, nonsteroidal anti-inflammatory drugs, ketamine, and α_2-δ ligands) may have an opioid-sparing effect when utilized alone, they may not effectively reduce opioid-related side effects[57,58,60,71,72,122]. Unfortunately, many of the investigators assessing opioid-related adverse effects used methodology that does not accurately reflect conditions in actual clinical practice. Nonsteroidal anti-inflammatory drugs are more likely to be used in multiple doses (which provide analgesia that is superior to that resulting from a placebo)[60] than in single doses for the management of postoperative pain. In addition, a more comprehensive multimodal approach, rather than bimodal therapy, is probably needed to reduce opioid-related adverse events and improve functional outcomes.

The importance of utilizing a multimodal rather than a bimodal approach for postoperative pain management was recently demonstrated in a study of spinal fusion surgery[124]. While the administration of either celecoxib or pregabalin alone reduced morphine use, neither reduced opioid-related side effects. In contrast, the combination of these two analgesics reduced both morphine use and the prevalence and severity of opioid-related side effects[126].

The beneficial effects of multimodal analgesia have also been demonstrated for patients treated with total knee arthroplasty[19-21]. In a randomized, placebo-controlled, double-blind trial, Buvanendran et al.[19] evaluated the effect of regional anesthesia and analgesia combined with a preoperative and thirteen-day postoperative course of treatment with a COX-2 inhibitor on opioid consumption and outcomes following total knee arthroplasty. The patients who received the COX-2 inhibitor had reductions in epidural analgesic use, in-hospital opioid consumption, pain scores, postoperative vomiting, and sleep disturbance as well as increased satisfaction as compared with patients treated with a placebo. In addition, an improved range of motion of the knee was observed both at the time of discharge and at one month after the surgery in the group treated with the sustained perioperative COX-2 inhibition.

The use of multimodal analgesia has also been found to be efficacious for patients treated with anterior cruciate ligament surgery[20]. Patients who were treated with a regimen of perioperative acetaminophen, rofecoxib, intra-articular analgesics (bupivacaine, clonidine, and morphine), a femoral nerve block, and postoperative cryotherapy had reduced prevalences of pain, opioid use, and postoperative nausea and vomiting; a shorter stay in the recovery room; and fewer unplanned readmissions to the hospital. In addition, this multimodal regimen effectively reduced the prevalence of long-term patellofemoral complications, including anterior knee pain, flexion contracture, quadriceps weakness, and chronic regional pain syndrome[21].

Prevention of Chronic Postoperative Pain Syndromes

Preemptive multimodal analgesic techniques appear to be promising for the treatment of acute postoperative pain and may reduce the prevalence of chronic pain following orthopaedic surgery[21]. The following is a summary of analgesic techniques aimed at reducing the prevalence of complex regional pain syndrome, phantom limb pain, chronic donor-site pain, and persistent pain following total joint arthroplasty.

Complex Regional Pain Syndrome

Complex regional pain syndrome is a disorder characterized by the presence, following a noxious event, of regional pain and sensory changes such as temperature alterations, abnormal skin color, abnormal sudomotor activity, and/or edema[127]. Its onset is associated with a history of trauma (that is often innocuous) or immobilization, and there is typically no correlation between the severity of the initial injury and the ensuing painful syndrome[128]. The Consensus Conference of the International Association for the Study of Pain has identified two forms of complex regional pain syndrome: type I (formerly known as reflex sympathetic dystrophy) and type II (formerly known as causalgia)[129]. A recent consensus guideline panel provided diagnostic clinical and research criteria with high sensitivity and specificity[130]. Patients with type-I or II complex regional pain syndrome can have sympathetically maintained pain or sympathetically independent pain[131].

The prevalence of complex regional pain syndromes occurring after an operation is variable and may be underreported[33]. Approximately 20% of patients who present to chronic pain clinics with complex regional pain syndrome have a history of an operative procedure in the affected area[132]. Most reported cases of postoperative complex regional pain syndrome have occurred after orthopaedic procedures, especially those on the extremities[33,132,133]. The estimated prevalences have ranged from 2.3% to 4% following arthroscopic knee surgery, 2.1% to 5% following carpal tunnel surgery, 13.6% following ankle surgery, 0.8% to 13% following total knee arthroplasty, 7% to 37% following wrist fractures, and 4.5% to 40% following fasciectomy for Dupuytren contracture[33].

Since type-II complex regional pain syndrome is the result of a definable nerve lesion[129], utilizing a surgical technique that minimizes the risk of nerve damage is an important factor in preventing the development of this syndrome following surgery[33]. Nerve injury may occur intraoperatively as a result of direct surgical trauma or excessive retraction or it may occur postoperatively as a result of nerve compression secondary to edema, hematoma, infection, or the application of tight dressings. Therefore, many cases of complex regional pain syndrome can be prevented by "careful technique, knowledge of anatomy, and proper postoperative management."[134] Furthermore, early recognition of the syndrome in the postoperative period is the key to facilitating successful treatment[33].

The use of a regional nerve block that provides a perioperative sympathectomy may be advantageous for patients with a history of complex regional pain syndrome who require orthopaedic surgery. It has been our practice to administer a stellate ganglion block to patients with complex regional pain syndrome who are undergoing upper-extremity surgery with local or general anesthesia. We previously performed a retrospective study of 100 patients with complex regional pain syndrome who underwent surgery on the affected upper extremity[135]. Half of the patients underwent a stellate ganglion block after completion of the operative procedure, and the other half received no intervention after the procedure. During the twelve-month period following the surgery, the rate of recurrence of the complex regional pain syndrome was significantly lower ($p < 0.01$) in the patients who had received the perioperative stellate ganglion block (five of fifty; 10%) than in those who had not (thirty-six of fifty; 72%).

In addition to stellate ganglion blocks, the perioperative sympathectomy provided by either a brachial plexus block or intravenous regional anesthesia with clonidine may provide a benefit to patients undergoing an operative procedure on the upper extremity. We previously showed that intravenous regional anesthesia with lidocaine and clonidine (1 μg/kg) is an effective way to manage both acute postoperative pain[40] and the symptoms of complex regional pain syndrome[42,43]. A prospective study of four anesthetic techniques (general anesthesia, intravenous regional anesthesia with lidocaine, intravenous regional anesthesia with lidocaine and clonidine, and an axillary block) in a series of 300 consecutive patients undergoing fasciectomy for the treatment of Dupuytren contracture confirmed a beneficial effect of the latter two techniques[136]. Postoperative complex regional pain syndrome developed in significantly ($p < 0.01$) more patients in the group treated with general anesthesia (twenty-five; 24%) and the group treated with intravenous regional anesthesia with lidocaine (twelve; 25%) than in either the group treated with an axillary block (five; 5%) or the group treated with intravenous regional anesthesia with lidocaine and clonidine (three; 6%).

In addition to perioperative regional blocks, pharmacologic agents including calcitonin, mannitol, vitamin C, corticosteroids, carnitine, and ketanserin have been advocated for the prevention of postoperative complex regional pain syndrome[33]. Interestingly, only vitamin C has been shown to be beneficial in prospective, placebo-controlled studies[137,138]. Vitamin C is a natural antioxidant that is reported to scavenge both hydroxyl radicals[139] and superoxide radicals that produce hydroxyl and other free radicals[140] that may be responsible for the pathogenesis of complex regional pain syndrome. Zollinger et al.[137] evaluated the efficacy of administering either 500 mg of vitamin C or a placebo daily for fifty days to 123 adults with a total of 127 wrist fractures. There was a significant ($p < 0.001$) reduction in the prevalence of complex regional pain syndrome in the vitamin-C group (7%) compared with the placebo group (22%) at the time of follow-up, at one year. Cazeneuve et al.[138] confirmed the benefits of vitamin C in a prospective, nonrandomized study of 195 patients with a wrist fracture who presented for surgery. Patients who received vitamin C (1 g daily) for forty-five days, starting on the day of the fracture, had a fivefold lower prevalence of complex regional pain syndrome (2.1% compared with 10% in patients who did not receive vitamin C; $p < 0.01$). This simple, safe, and inexpensive technique may have important implications in the development of protocols for the prevention and management of complex regional pain syndrome.

Finally, preventive multimodal analgesic techniques in conjunction with physical therapy and rehabilitation following an operation appears to be a promising technique for reducing the prevalence of postoperative complex regional pain syndrome. Patients who were treated with a regimen of peri-

operative acetaminophen, rofecoxib, intra-articular analgesics (bupivacaine, clonidine, and morphine), a femoral nerve block, and postoperative cryotherapy demonstrated a significant ($p < 0.001$) reduction in the prevalence of complex regional pain syndrome at one year following anterior cruciate ligament surgery[21].

Phantom Limb Pain

Patients who experience the loss of a limb, either traumatically or surgically, almost always report some degree of perceived sensation in the lost limb. A distinction should be made between phantom limb pain (painful sensations referred to the absent limb), phantom limb sensation (any sensation in the absent limb, except pain), and stump pain (pain localized in the stump), although each may be felt by an individual patient at different times[141]. Recent reports have suggested that the prevalence of phantom pain is probably between 50% and 80%[142-144]. Several risk factors have been identified for the development of phantom limb pain, including the degree of preoperative pain, the magnitude of intraoperative noxious input, the intensity of postoperative pain, and psychological factors[1,145].

The mechanisms of phantom pain are not completely clear. As is the case with other types of neuropathic pain, there are likely both peripheral and central factors at play. Increased spontaneous activity of both afferent peripheral nerves and dorsal root ganglion cells has been observed experimentally following the transection of a nerve[6]. In addition, the sympathetic nervous system may have a role in sensitizing and maintaining the abnormal afferent output from damaged nerve fibers after amputation[6]. It is now known that the central nervous system undergoes substantial functional reorganization following amputation[146].

Several investigations have focused on the use of preventive regional analgesic techniques to reduce perioperative pain and phantom pain following surgical amputation of the lower extremity[147]. Bach et al.[148] compared the effect of epidural morphine or bupivacaine, or both in combination, used for three days before the amputation in eleven patients with that of conventional analgesia in fourteen patients. After six months, all patients in the epidural group were pain-free whereas five patients in the control group had phantom pain ($p < 0.05$). Jahangiri et al.[149] confirmed the beneficial effects of perioperative epidural analgesics for preventing phantom pain following amputation surgery in a study in which an epidural infusion of bupivacaine, diamorphine, and clonidine had been administered to thirteen patients for twenty-four to forty-eight hours preoperatively and maintained for at least three days postoperatively. For comparison, a control group of eleven patients received on-demand opioid analgesia. The authors observed a significant ($p < 0.01$) reduction in the prevalence of phantom pain at one year following the operation in the patients treated with the epidural infusion. However, what we believe to be the largest prospective study of the effect of epidural analgesia on phantom pain (sixty patients) failed to document any benefit[150]. This study may be criticized, however, because the investigators chose to provide preemptive epidural analgesia for only eighteen hours prior to the amputation.

Similarly, the results of clinical investigations of the efficacy of continuous postoperative regional analgesia with a nerve sheath block following amputation surgery have been equivocal, with some studies revealing beneficial effects[151,152] and others demonstrating no long-term benefit[153,154]. In one study, a preoperative epidural block with bupivacaine and diamorphine was found to prevent phantom pain as effectively as infusion of bupivacaine from an intraoperatively placed perineural catheter, but the epidural analgesic technique was more effective in relieving stump pain in the immediate postoperative period[155].

Unfortunately, many of the studies evaluating the ability of regional analgesics to reduce long-term phantom pain have had multiple design flaws, including not being prospective, not being randomized or blinded, either not including a control group or using historical controls, involving a heterogeneous study group, or lacking sufficient power. The authors of a recent systematic review of the literature concluded that, because of poor quality and contradictory results, the randomized and controlled trials that have been reported do not provide evidence to support any particular treatment of phantom limb pain in the acute perioperative period or later[147].

Chronic Donor-Site Pain

Chronic pain is not an uncommon complication following spinal fusion surgery. Autogenous bone grafts are frequently harvested from the ilium for the purposes of bone fusion in patients undergoing spinal stabilization surgery. Often, the pain from the donor site is more severe than that from the operative site in the spine[156-159]. Although this pain usually resolves over a period of several weeks, it may persist and represent a source of postoperative morbidity[156-159]. In fact, donor site pain has been reported in up to 39% of patients at three months, 38% at six months, 37% at one year, and 19% at two years after harvesting of bone graft from the iliac crest[157-160].

The precise mechanism of donor site pain remains obscure. It has been postulated to be muscular or periosteal in nature, secondary to stripping of the hip abductors from the ilium[156]. In addition, the pain may be neuropathic in origin, secondary to injury to small sensory nerves at the donor site. Two nerves that are frequently injured during the harvest of bone graft from the anterior aspect of the ilium are the lateral femoral cutaneous and ilioinguinal nerves[156]. The superior cluneal nerves pierce the lumbodorsal fascia and cross the posterior iliac crest 8 cm lateral to the posterior superior iliac spine[161]. These nerves may be injured while bone graft is harvested from the posterior aspect of the ilium, and the injury may result in transient or permanent numbness and pain over the buttock area.

Three recent studies have demonstrated a substantial reduction in the prevalence of chronic donor-site pain with the preemptive administration of analgesics[160,162,163]. Houghton et al.[164] showed that the local application of a low dose of morphine effectively blocked the development of hyperalgesia and allodynia in a rat model of bone damage. This analgesic effect

was considered to be mediated through μ-opioid receptor action in the bone. Gündes et al.[163] infused 20 mL of saline solution alone, a solution containing 50 mg of bupivacaine, or a solution containing 50 mg of bupivacaine and 5 mg of morphine through a 17-gauge catheter placed at the iliac crest donor site in forty-five patients undergoing spinal fusion surgery. These investigators reported the absence of chronic donor-site pain at twelve weeks in the group treated with bupivacaine and morphine, whereas five of fifteen patients who had received the saline solution alone and two of fifteen patients treated with the bupivacaine alone had such pain.

We subsequently evaluated the analgesic effect of low-dose morphine alone administered to the site of bone-graft harvesting in patients undergoing spinal fusion surgery[160]. Of the sixty patients in the study, twenty were randomized to be treated with infiltration of saline solution into the harvest site; twenty, with 5 mg of intramuscular morphine; and twenty, with infiltration of 5 mg of morphine into the harvest site (twenty patients in each group). Infiltration of morphine into the bone graft harvest site significantly reduced the pain scores and opioid use for the first twenty-four hours following surgery ($p < 0.0001$). Furthermore, the prevalence of chronic donor-site pain was significantly lower ($p < 0.05$) in the group that had received local morphine (5%) than in those treated with intramuscular morphine (37%) or infiltration of saline solution (33%).

We also examined the analgesic effects of preemptive COX-2 administration on chronic donor-site pain following spinal fusion surgery[162]. It has been shown that COX-2 plays an integral role in the processes of peripheral and central sensitization[165], and it is possible that early and sustained treatment with COX-2 inhibitors may thwart the progression of acute to chronic pain[166]. Eighty patients scheduled to undergo posterior spinal fusion with instrumentation were randomized either to receive 400 mg of celecoxib one hour prior to surgery followed by 200 mg every twelve hours postoperatively for the first five days or to receive a matching placebo at similar time intervals[162]. The prevalence of chronic donor site pain was significantly higher ($p < 0.01$) in the placebo group (twelve of forty patients; 30%) than in the celecoxib group (four of forty patients; 10%) at one year following surgery.

These three studies[160,162,163] highlight the importance of utilizing preemptive analgesics for management of pain following spinal fusion surgery. We currently administer 1000 mg of acetaminophen, 400 mg of celecoxib, and 150 mg of pregabalin one to two hours before spinal fusion surgery. Intraoperatively, 20 mg of ketamine is administered intravenously and the graft harvest site is infiltrated with a mixture of 10 mL of 0.25% bupivacaine, 5 mg of morphine, and 50 μg of clonidine. Patients then receive 200 mg of celecoxib and 75 mg of pregabalin twice daily, 1000 mg of acetaminophen four times daily, and 10 mg of controlled-release oxycodone twice daily for the first week postoperatively. We are currently examining the efficacy of this preemptive multimodal analgesic technique for reducing acute and chronic pain. Additional studies are needed to assess the appropriate dosages, timing, and duration of various preventive analgesic techniques to reduce chronic donor-site pain.

Chronic Pain After Total Joint Arthroplasty

Total joint arthroplasty has proved to be a successful operative treatment of hip and knee joints affected by osteoarthritis. In 2003, more than 400,000 total knee arthroplasties and 220,000 total hip arthroplasties were performed in the United States, with reported success rates ranging from 80% to 90%[167]. A recent nationwide Danish study revealed that 28.1% of more than 1200 consecutive patients who had undergone total hip arthroplasty reported having chronic ipsilateral hip pain twelve to eighteen months after the operation[168]. Furthermore, this persistent hip pain limited daily activity to a moderate-to-severe degree in 12.1% of these patients. In a prospective observational study, 18.4% of patients reported moderate-to-severe pain at six months following a total knee arthroplasty and 13.1% reported such pain at one year[169]. Defining who is at risk for the development of chronic pain following total joint arthroplasty would be extremely useful in preventing this outcome.

Severe preoperative pain is a primary indication for total joint arthroplasty[167], but it is also the primary predictor of chronic postoperative pain[1]. Higher pain ratings before rehabilitation predict treatment failure and are associated with poor outcomes in patients with chronic musculoskeletal disorders[170]. Patients with greater preoperative pain were found to be at greater risk for heightened postoperative pain after total joint arthroplasty irrespective of confounding issues, such as the severity of the preoperative disease or postoperative complications[169,171,172]. Greater preoperative pain also leads to worse Knee Society function scores at one year postoperatively and is associated with a longer hospital stay, longer inpatient rehabilitation, a lower range of motion, more postoperative knee manipulations, and more home physical therapy visits[169]. Furthermore, greater preoperative pain intensity is a significant predicting factor ($p < 0.01$) for the development of complex regional pain syndrome at three and six months following total knee arthroplasty[172].

Preoperative psychological factors may also play a role in the development of persistent pain following operative procedures[1], including total knee arthroplasty[169,172]. Psychosocial variables seem to be an important factor in the pain response and can lead to a poor functional outcome in patients with osteoarthritis of the knee[173,174]. Two recent prospective studies have confirmed that preoperative depression and anxiety are associated with a higher prevalence of chronic pain and complex regional pain syndrome after total knee arthroplasty[169,172]. Because there are psychosocial risk factors for severe acute pain[1] and because psychosocial and pharmacologic interventions can reduce pain and psychosocial distress, the best preventive intervention may be one that combines pharmacologic and psychosocial treatments. Therefore, strategies aimed at screening, identifying, and treating patients with depression, anxiety, and severe pain before an operation may be important to prevent the development of chronic pain and improve outcomes following total joint arthroplasty.

Overview

The development of chronic pain continues to be a major source of morbidity following a variety of orthopaedic surgical procedures. Despite its prevalence, our understanding of chronic postoperative pain and the potential means of risk reduction are somewhat deficient. Preventive multimodal analgesic techniques may play a role in reducing the prevalence of certain chronic postoperative pain syndromes. The appropriate timing of analgesic intervention in the perioperative period is an important factor to understand. In order to effectively prevent the development of central neuroplasticity, it is necessary to administer analgesics during the preoperative, intraoperative, and postoperative periods. Furthermore, regional blockade by itself may not be sufficient to provide complete pain relief and prevent central sensitization. It has been demonstrated that, despite adequate neural blockade during surgery, central prostaglandin synthesis can still be induced, potentially leading to central neuroplasticity and increased postoperative pain[175]. A multimodal analgesic regimen utilizing regional blockade, nonsteroidal anti-inflammatory drugs, and other peripheral and centrally acting analgesics, including α-2 agonists, ketamine, α_2-δ ligands, and opioids, administered throughout the perioperative period may be the most efficacious strategy for reducing both acute and chronic pain following orthopaedic surgery. Future large-scale randomized, controlled trials are necessary to better understand the use of preventive multimodal analgesic techniques in reducing chronic postoperative orthopaedic pain syndromes.

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