One of the most common concerns reported by patients before surgery is the presence of postoperative pain.1 Evidence reveals, however, that adequate postoperative analgesia is achieved in a minority of patients.2 Despite national healthcare policy recommendations and clinical guidelines encouraging aggressive management of postoperative pain,3 the incidence of inappropriate pain control has not changed significantly in recent years.1,4 A recent study conducted in a cohort of adult surgical patients in the United States found that 86% experienced pain after surgery, of which 75% had moderate-to-severe pain in the immediate postoperative period, and 74% experienced similar levels of pain even after discharged home.5 Similar observations have been reported by 2 previous studies performed more than a decade ago.1,6 These studies reveal that recent advances in surgical and analgesic techniques have had little clinical effect in the practice of postoperative pain management.

Unrelieved postoperative pain is linked to adverse physiological changes that eventually might translate in adverse postoperative outcomes, including increased morbidity and mortality.7 Furthermore, the limitation of movement caused by pain can prolong rehabilitation, reduce health-related quality of life, and delay return to normal daily activities.8–11 Increased cost of care, extended hospital length of stay, readmissions of inpatients or unexpected admissions to hospital of outpatients, and patient dissatisfaction

**Summary:** To improve postoperative pain management, several concepts have been developed, including preemptive analgesia, preventive analgesia, and multimodal analgesia. This article will discuss the role of these concepts in improving perioperative pain management. Preemptive analgesia refers to the administration of an analgesic treatment before the surgical insult or tissue injury. Several randomized clinical trials have, however, provided equivocal evidence regarding the benefits of preincisional compared with postincisional analgesic administration. Current general consensus, therefore, indicates that use of preemptive analgesia does not translate into consistent clinical benefits after surgery. Preventive analgesia is a wider concept where the timing of analgesic administration in relation to the surgical incision is not critical. The aim of preventive analgesia is to minimize sensitization induced by noxious stimuli arising throughout the perioperative period. Multimodal analgesia consists of the administration of 2 or more drugs that act by different mechanisms for providing analgesia. These drugs may be administered via the same route or by different routes. Thus, the aim of multimodal analgesia is to improve pain relief while reducing opioid requirements and opioid-related adverse effects. Analgesic modalities currently available for postoperative pain control include opioids, local anesthetic techniques [local anesthetic infiltration, peripheral nerve blocks, and neuraxial blocks (epidural and paravertebral)], acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2-specific inhibitors as well as analgesic adjuncts such as steroids, ketamine, α2 agonists, and anticonvulsants. (Plast. Reconstr. Surg. 134: 85S, 2014.)
are common consequences of these adverse outcomes. Nevertheless, one of the most often misdiagnosed and neglected consequences of inadequately treated pain after surgery is persistent postoperative pain (PPP). Evidence suggests that acute postoperative pain is a major risk factor for the development of PPP.

Knowing the deleterious physiological effects and outcomes from inadequately treated acute postoperative pain, the natural sound ensuing question is why have clinicians not been sufficiently successful in management of postsurgical pain? The causes could be multifactorial, but 2 important points need to be emphasized. First, pain is a complex multidimensional sensory experience that includes both sensation and strong cognitive and emotional components. And second, the mechanisms of pain are also multifactorial, and many of those still need to be defined. Therefore, inadequate treatment of postoperative pain can be attributed, at least in part, to the incomplete understanding by clinicians of the basic mechanisms of postsurgical pain and the inadequate use of current concepts in pain management.

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**PREEMPTIVE ANALGESIA**

Preemptive analgesia refers to the administration of an analgesic treatment before the surgical insult (incision) or tissue injury. The concept of preemptive analgesia is based on well-recognized pathophysiology of surgical pain, which includes peripheral and central sensitization. In brief, peripheral sensitization occurs when inflammatory mediators released at the wound site decrease the threshold of terminal nerve endings, leading to enhancement of nociceptive pain. Central sensitization results from an enhanced response that is provoked by hyperexcitability of the neurons in the dorsal horn of the spinal cord secondary to intense afferent impulses originated in the site of injury. Peripheral and central sensitizations are manifested clinically as an increasing sensitivity to pain at the site of injury or inflammation.

Central and peripheral sensitizations are the major causes of hypersensitivity to pain after injury. Therefore, in theory, blocking the surgical noxious impulses should reduce the amplification of the nociceptive signals, making timing of analgesic administration an important aspect of pain management. A report from Woolf published in 1986 provided evidence in support of this theory and led to a series of clinical investigations comparing analgesic techniques administered before versus after surgical incision. Some reports showed reduction in analgesic demand and pain scores in the immediate postoperative period as a result of preoperative administration of several analgesic techniques. However, several randomized clinical trials provide equivocal evidence regarding the benefits of preincisional compared with postincisional analgesic administration, indicating that the effectiveness of preemptive analgesia is debatable. The majority of randomized clinical trials comparing the effect of preoperative versus postoperative administration of various drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, N-methyl-d-aspartate (NMDA) receptor antagonists, and local anesthetics given by local infiltration, intraarticular, nerve block, or epidural routes, have not demonstrated significant improvement in pain outcome measures. The reasons for lack of benefit of those reports may include use of a single medication (in contrast to a multimodal approach) or the use of a single dose of the analgesic, which may have resulted in inadequate duration of analgesia leading to peripheral and/or central sensitization after the drug effect has worn out. Current general consensus, therefore, indicates that use of preemptive analgesia does not translate into major or consistent clinical benefits after surgery. Thus, the timing of analgesic administration does not have to be related to the surgical incision.

**PREVENTIVE ANALGESIA**

In contrast to preemptive analgesia, which involves administration of the analgesic before surgical intervention, preventive analgesia is a wider concept. The aim of preventive analgesia is to minimize sensitization induced by noxious stimuli arising intraoperatively and postoperatively. An analgesic intervention is defined as preventive when it fulfills 2 characteristics. First, it is able to reduce the degree of postoperative pain and/or the amount of analgesic consumption compared with another treatment, placebo, or no treatment. Second, the duration of the effect of the intervention exceeds the clinical duration of action of the target drug. It is generally accepted that the pharmacological activity of a drug is not
clinically significant when at least 5.5 half-lives of the target drug have elapsed since its administration. Accordingly, preventive analgesia implies that the effect on pain control of the intervention extends beyond its analgesic effect (ie, beyond 5.5 half-lives of the drug). Thus, an intervention can be initiated either intraoperatively or postoperatively and still demonstrate preventive effects. For example, a study on patients undergoing iliac crest bone grafting demonstrated that an infusion of ropivacaine started postoperatively into the iliac crest harvest site reduced acute pain and morphine consumption within 48 hours postoperatively as compared with saline. Most importantly, pain scores on movement were significantly lower in the ropivacaine-treated group 3 months after surgery, demonstrating a preventive analgesic effect of ropivacaine.

A recent systematic review of literature examined studies assessing preventive analgesia with peripheral nerve blocks, transversus abdominis plane blocks, and intravenous (IV) lidocaine infusion. The authors found that in most of the included studies, use of local anesthetic techniques reduced postoperative pain scores and opioid requirements. However, the addition of adjuvants to local anesthetics did not consistently show any analgesic benefits. Importantly, there were no apparent differences in administration of analgesics preoperatively, intraoperatively, or postoperatively. Thus, these observations could not show any preemptive analgesic analgesia.

**MULTIMODAL ANALGESIA**

The concept of multimodal analgesia was developed based on the knowledge that postoperative pain is a complex and multifactorial phenomenon. Therefore, it seems reasonable that instead of using a single medication or technique, combinations of analgesics of different classes acting on different target sites may provide superior pain relief with lower incidence of adverse effects. Multimodal analgesia can be defined as the administration of 2 or more drugs that act by different mechanisms for providing analgesia. These drugs may be administered via the same route or by different routes. Thus, the aim of multimodal analgesia is to improve pain relief while reducing opioid requirements and opioid-related adverse effects.

Analgesic modalities currently available for postoperative pain control include opioids, local anesthetic techniques [local anesthetic infiltration, intraarticular, peripheral nerve blocks, and neuraxial blocks (epidural and paravertebral)], acetaminophen, NSAID, and cyclooxygenase (COX)-2-specific inhibitors as well as analgesic adjuncts such as steroids (eg, dexamethasone), NMDA antagonists (eg, ketamine), α-2 agonists (eg, clonidine and dexmedetomidine), and anti-convulsants (eg, gabapentin and pregabalin).

**Opioids**

Opioids are effective for treatment of moderate-to-severe pain and commonly used for treatment of postoperative pain in the United States. However, many dose-related adverse effects, including nausea, vomiting, itching, prolonged ileus, urinary retention, dizziness, drowsiness, and most importantly, respiratory depression, limit the use of opioids. In addition, use of high doses of opioids can produce acute tolerance and hyperalgesia within a few hours of administration. Therefore, it is recommended that the use of opioids should be reserved for treatment of severe pain as a component of multimodal analgesia.

**Local Anesthesia Techniques**

Local anesthetic techniques include neuraxial analgesia (eg, epidural and paravertebral block) and peripheral nerve blocks as well as wound infiltration. These approaches provide excellent dynamic pain relief and reduce opioid requirements. Therefore, local anesthetic techniques should be the primary component of multimodal analgesia technique and should be used whenever possible. Because long-acting local anesthetics (eg, bupivacaine, levobupivacaine, and ropivacaine) provide a prolonged duration of analgesia, they are preferred. A long-acting formulation of bupivacaine (liposomal bupivacaine) has been shown to provide excellent pain relief for up to 72 hours after wound infiltration, but its use is not approved for peripheral nerve block.

The combination of local anesthetics and opioids for epidural techniques provides superior analgesia than any of the drugs alone. However, the addition of opioids to epidural local anesthetics increases the incidence of pruritus with uncertain benefit in the reduction of nausea and vomiting. Furthermore, recent systematic reviews and meta-analyses have reported conflicting results with regard to the role of epidural analgesia in improving perioperative outcome and duration of hospital stay. Therefore, epidural analgesia is currently reserved for thoracic and upper abdominal surgical procedures.
Peripheral nerve blocks provide site-specific analgesia and thus avoid the adverse effects associated with neuraxial blockade (eg, hypotension, urinary retention, and motor paresis leading to delayed ambulation). The introduction of ultrasound technology has improved the success rate of block placement and possibly associated complications. However, single-injection peripheral nerve blocks are limited by the relative short duration of action of the local anesthetic (usually 12–18 hours) and abrupt termination of analgesia. This limitation can be overcome by using continuous perineural infusion of local anesthetic.

Concerns of peripheral nerve block, particularly in the blocks of lower extremity, include motor blockade, resulting in delayed ambulation and increased potential for falls.70

Use of surgical wound infiltration techniques has increased in recent years, with several studies reporting benefits of local anesthetic infusion in the surgical wound and the preperitoneal space.71,72 These techniques provide excellent analgesia with negligible adverse effects. In addition, the availability of long-acting liposomal bupivacaine further enhances the efficacy of the wound infiltration techniques. The longer duration of liposomal bupivacaine obviates the need for use of continuous infusion of bupivacaine.

Use of IV lidocaine infusion intra- and postoperatively is another technique that has been evaluated. Current evidence reveals that lidocaine infusion can provide excellent pain relief and reduce opioid requirements as well as opioid-related side effects.73,74 Interestingly, the analgesia provided by IV lidocaine infusion has been reported to be similar to that provided by epidural analgesia.

Acetaminophen

Acetaminophen is a weak analgesic suitable for the treatment of mild-to-moderate pain.75,76 Its efficacy can be significantly enhanced by using appropriate doses (ie, 1 g every 6 hours, maximum 4 g/d) and by combination with NSAID or COX-2 inhibitors.77,78 An IV formulation of acetaminophen has been recently approved by the Food and Drug Administration for perioperative use. The IV route allows for a rapid and predictable increase in plasma and cerebrospinal fluid concentrations, allowing a reliable use as part of a multimodal approach. Several recent studies have demonstrated the effectiveness of IV acetaminophen in decreasing postoperative pain scores and morphine consumption after variety of surgical procedures.79–86 Although it is generally considered safe and devoid of some of the side effects of nonselective NSAID,75,76 acetaminophen is associated with liver and gastrointestinal toxicity at high doses.87,88

Nonsteroidal Anti-Inflammatory Drugs and Cyclooxgenase-2-Specific Inhibitors

Nonselective NSAID and COX-2-specific inhibitors play an important role in prevention of peripheral and central sensitization.17 Several meta-analyses have provided evidence that these analgesics improve pain scores and reduce opioid requirements.89–93 Despite the proven analgesic benefits, its use is limited by the risk of perioperative complications, including bleeding, gastric irritation/ulceration, impairment of wound and bone healing, and bronchospasm in patients with reactive airway disease. Although nonselective NSAIDs have been associated with increased blood loss,94–96 COX-2-specific inhibitors have no effects on platelet function, and thus do not increase the risk of perioperative bleeding.83,97,98 The risk of renal dysfunction is very low in patients with normal preoperative renal function receiving short courses of NSAID. However, in the elderly, in patients with impaired renal function, or in the presence of concomitant renal risk factors (eg, hypovolemia, hypotension, and use of angiotensin-converting enzyme inhibitors or nephrotoxic agents), the risk of renal adverse effects is increased.99 Finally, in about 10–15% of patients with asthma, aspirin and NSAID, but not COX-2-selective inhibitors, may provoke episodes of bronchospasm.100

A more recent formulation of NSAIDs includes intranasal (IN) ketorolac spray. IN ketorolac has demonstrated superior analgesia compared with placebo in patients undergoing third molar extraction101 and decreased morphine consumption as well as a higher quality of analgesia scores after abdominal surgery.102 IN ketorolac has a more rapid onset of action than the oral formulation and may be an alternative for pain management in ambulatory surgery.

Glucocorticoids

The analgesic effect of glucocorticoids is attributed to their effects on reducing the inflammatory response to surgical stress by blocking the COX and lipooxygenase enzymes. A recent meta-analysis revealed that a single-dose dexamethasone administered either preoperatively or intraperatively significantly reduced postoperative pain,
opioid consumption, need for rescue analgesia, recovery room stays, and prolonged the time to first analgesic dose without increasing the risk of infection or delayed wound healing.103 Dexamethasone was, however, associated with mild increases in blood glucose on the first postoperative day. Because dexamethasone reduces postoperative pain as well as nausea and vomiting, it should be used whenever possible.

**N-Methyl-d-Aspartate Antagonists**

Ketamine is an NMDA receptor antagonist with effects on central sensitization and neural modulation.53,104 Given its high affinity for NMDA receptors, only small doses of ketamine (about one tenth of the anesthetic dose) are needed to decrease the likelihood of central sensitization.105 The beneficial effect of ketamine seems to persist beyond the pharmacologic action of the drug, thus providing preventive analgesia.

Several meta-analyses have shown that a subanesthetic dose of ketamine can be an effective adjunct to opioids, local anesthetics, and other analgesics for postoperative pain management.106,107 The recommended dose of ketamine for multimodal analgesia consists of a bolus of 250–500 μg/kg followed by an infusion of 0.2–0.3 mg/kg/h (about 4–5 μg/kg/min).108 Postoperative continuation of the infusion, when possible, is recommended because it can decrease pain scores in the postoperative period.109 Because of lack of consistent benefits, ketamine may be reserved for situations where routine analgesics are ineffective or limited by their side effects, such as major surgical procedures, patients on prolonged opioids, and those at high risk of PPP. Although rarely at low doses, adverse effects of ketamine include hypertension, tachycardia, and psychomimetic effects including hallucinations, nightmares, and cognitive dysfunction.

**α-2 Agonists**

α-2 agonists have sedative and analgesia-sparing effects via central actions in the locus ceruleus and in the dorsal horn of the spinal cord, respectively.110 The analgesic benefits of clonidine remain controversial, and available studies reveal equivocal evidence of the effect of clonidine on postoperative pain scores.3,111–114 In addition, clonidine is limited by its side effects including bradycardia, hypotension, and excessive sedation. Compared with clonidine, dexmedetomidine is more selective and has a shorter duration of action. Dexmedetomidine does not cause respiratory depression, despite its potent sedative effects. Because of its opioid-sparing effects,115 it is increasingly used in patients at high risk of airway obstruction and respiratory depression associated with opioids (eg, patients with sleep apnea and morbid obesity). Used as part of a multimodal analgesic plan in morbidly obese patients undergoing bariatric surgery, an intraoperative infusion of dexmedetomidine decreased postoperative opioid consumption, incidence of postoperative nausea/vomiting, and the length of stay in the recovery unit.116

**Gabapentinoids**

Gabapentinoids (ie, gabapentin and pregabalin) are frequently used for treatment of neuropathic pain.117–120 Although gabapentinoids have a chemical structure similar to gamma-aminobutyric acid, their antihyperalgesic effects are exerted through interactions with the α-2-delta subunit of voltage-dependent calcium channels.122 Gabapentinoids inhibit central sensitization through presynaptic or postsynaptic inhibition of calcium influx, which inhibits the release of neurotransmitters from the primary afferent nerve fibers in the spinal cord.123 Gabapentinoids have received great attention because of demonstration of preventive analgesic effects lasting months after surgery.124–126 A recent meta-analysis demonstrated the effectiveness of gabapentin and pregabalin on prevention of chronic postsurgical pain, defined as persistent pain more than 2 months after surgery,127 supporting the idea that pregabalin and gabapentin have important preventive analgesic effects.

**SUMMARY**

Although preemptive analgesia has been shown to have significant analgesic benefits in animal models, clinical studies have not been able to show clinically relevant effects. Therefore, the timing of analgesic administration should depend upon the pharmacokinetics of the drug and type of surgical procedure. Use of multimodal analgesia techniques should be the standard approach for any surgical pain management protocol. The choice of analgesic combinations should not only depend on their analgesic efficacy but also on the overall side effect profile of these combinations. Thus, even if a certain analgesic regimen provides superior pain relief, it may not be clinically beneficial if it is also associated with more adverse events. It is recommended that local/regional analgesia should be used as the principal method in the multimodal analgesia technique.
Other nonopioid analgesics (e.g., acetaminophen, NSAID, or COX-2-specific inhibitors) should be used, assuming there are no contraindications. Opioids could be used as “rescue” analgesics on an “as-needed” basis rather than on a scheduled basis. However, there is a need for development of an evidence-based approach to comprehensive, individualized analgesic plans for specific surgical procedures.

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