Multimodal Analgesia: The Foundation of a Successful Perioperative Experience

ERIC S. SCHWENK, MD
Associate Professor of Anesthesiology
Sidney Kimmel Medical College
at Thomas Jefferson University
Philadelphia

EDWARD R. MARIANO, MD, MAS
Professor of Anesthesiology
Stanford University School of Medicine
Veterans Affairs Palo Alto Health Care System
Palo Alto, Calif., and
Member, Editorial Advisory Board, Anesthesiology News

Drs. Schwenk and Mariano reported no relevant financial disclosures.

Perioperative pain can be described as nociceptive, neuropathic, psychogenic or idiopathic, and mixed, and treatments should be tailored to the type of pain being experienced.

Introduction

The delivery of high-quality health care at the lowest possible cost is no longer an aspiration; it is the expectation. To illustrate this point, the Merit-Based Incentive Payment System (or MIPS) developed by the Centers for Medicare & Medicaid Services has replaced the former fee-for-service system with a new payment model based on a physician’s achievement of specific metrics to drive “incentives” and reward the delivery of cost-effective high-quality care.1

In the field of perioperative pain management, the implementation of multimodal analgesia in the pre-, intra- and postoperative periods is an effective and proven method of accomplishing this. Although slight variations exist, we will define “multimodal analgesia” as the use of several classes of analgesics with varying mechanisms of action used together to improve pain control, decrease overreliance on opioids for analgesia, and reduce side effects associated with each class.2
Multimodal analgesia should be considered the standard for perioperative pain management in most surgical patients. In this review, we present the basis for multimodal analgesia in a general context, next in the setting of the opioid crisis, and finally focusing on perioperative pain management for orthopedic surgery.

Components of Multimodal Analgesia And Challenges to Implementation

Because the characteristics of pain vary both between patients and within a given patient at different times, it is unreasonable to expect a single category of analgesics to adequately treat all pain. Perioperative pain can be described as nociceptive, neuropathic, psychogenic or idiopathic, and mixed; therefore, treatments should be tailored to the type of pain being experienced. In the case of preoperative multimodal analgesia, a combination of agents that treat both nociceptive and neuropathic pain works best.

The benefits of not relying on a single class of medications to treat pain were recognized several decades ago by Kehlet and Dahl, whose work established the basis for the “multimodal movement.” Consistency and standardization are important when implementing a multimodal analgesia pathway for a particular surgery. Standardization based on evidence allows for the largest number of patients to receive the best treatments available. Flexibility with protocols is also needed, allowing for tailoring of pain management to the individual patient, and alternative medications should be proposed to account for allergies, comorbidities and preferences.

In some cases, creating a protocol that recommends a class of medications is preferable to naming a specific agent. For example, recommending a nonsteroidal anti-inflammatory drug (NSAID) rather than specifying ketorolac may facilitate implementation and acceptance and improve adherence by both patients and clinicians, even if a patient previously had an adverse reaction to one drug in the class. The first choice medication within a drug class may be influenced by local factors such as formulary restrictions and supply chain considerations. Instructions on which alternative drugs to administer if the first choice is not preferred are useful and may be incorporated into written order sets.

Alternative drugs within classes are also needed in the era of drug shortages. This is particularly relevant for perioperative physicians because a majority of the IV medications used in the United States, including some perioperative medications, are made by a small number of pharmaceutical companies, emphasizing the dramatic downstream effects that a manufacturing problem within one company can create. Thinking outside the box may be necessary if a commonly used agent suddenly becomes unavailable.

Drugs used in anesthesia that have been listed as being in shortage by the American Society of Health-System Pharmacists include ketamine, fentanyl and hydromorphone, analgesics that are commonly part of multimodal regimens. When drugs that are less familiar to clinicians are substituted, medication errors can occur.

It can be argued that clinicians should familiarize themselves with acceptable alternatives by substituting them in clinical practice periodically and spending the necessary time to understand commonly used doses, frequencies and contraindications as well as the existing evidence supporting each agent.

Importance of Multimodal Analgesia in the Opioid Crisis

Never has the need for effective alternatives to opioids been greater than in the current health care situation, in which more than 42,000 Americans died of opioid-related causes in 2016. A retrospective study from Sun et al found that the risk for taking opioids chronically was increased in surgical patients compared with those not undergoing surgery. Similarly, Brummett et al observed an increased rate of long-term opioid use in surgical patients compared with nonsurgical patients, and their study did not report any substantive difference between major and minor surgeries.

Prescribing patterns of physicians undoubtedly play a major role in determining initial length of prescription, which in turn affects the likelihood of using long-term opioids after surgery, but this topic will not be discussed here. However, the perioperative period, and particularly the postoperative period of time leading up to the day of discharge, represents a potential window of opportunity when clinicians may be able to intervene to reduce pain. Providing better pain control and using other modalities that result in lower opioid doses should theoretically put surgeons and other prescribing physicians in a better position to reduce doses, write shorter prescriptions or both for patients after they leave the hospital. This remains to be proven, however, and indeed one study that examined this topic found that despite producing lower pain ratings and opioid use at the time of discharge, opioid-free surgery did not change discharge prescribing patterns.

The reasons for this inconsistency are multifactorial, and we believe this lack of evidence should not dissuade the anesthesiology and surgery communities from trying to minimize perioperative opioid use. This is a subject of ongoing research, but there are several other proven benefits of multimodal analgesia, such as decreased postoperative pain as well as reduced nausea and vomiting, that make the effort worthwhile.

Multimodal Analgesic Agents For Orthopedic Surgery

Orthopedic surgeons were relatively early adopters and proponents of multimodal analgesia. A study from 2002 described an opioid-free analgesic strategy after total knee arthroplasty (TKA), and many other studies soon followed. This may be partly because of the emphasis in orthopedic surgery on early ambulation and mobility. In a large, retrospective database study of patients who underwent total joint arthroplasty,
Memtsoudis et al found that each additional nonopioid analgesic produced a stepwise decrease in postoperative complications, with NSAIDs resulting in the greatest decrease.\textsuperscript{15} The most commonly used agents are discussed here.

**Acetaminophen**

Acetaminophen is one of the most well-known and well-studied analgesics and has been in clinical use for decades. Barring abnormal liver function, there are few, if any, contraindications. The total daily maximum dose is 4 g in a healthy adult, above which the risk for liver toxicity increases.\textsuperscript{16} The mechanism of action may be related to inhibition of cyclooxygenase (COX) pathways.\textsuperscript{16} Acetaminophen is a common and important part of multimodal analgesic regimens for orthopedic surgery, and we recommend routinely including it in both orthopedic and non-orthopedic pathways.\textsuperscript{17,18} The drug’s low cost and tolerability make it an attractive component of perioperative analgesia.\textsuperscript{19}

A meta-analysis of the analgesic effect of a single dose of acetaminophen for acute postoperative pain found that 36% of patients reported four hours of relief.\textsuperscript{20} Although not sufficient by itself, acetaminophen is a safe and reliable analgesic that can be given preoperatively, intraoperatively via the IV route, and postoperatively on a scheduled basis.

It is worth noting that there is insufficient evidence to support routine use of the IV route over the oral route of administration.\textsuperscript{21} However, some studies have shown benefit with the use of IV acetaminophen in patients undergoing total joint arthroplasty. A large database study found that IV acetaminophen was associated with a shorter hospital length of stay and fewer discharges to a skilled nursing facility.\textsuperscript{22} In a randomized controlled trial comparing IV and oral acetaminophen given perioperatively during total joint replacement, the authors found that the IV form improved pain ratings during the first four hours after surgery only; beyond that, it did not provide any additional analgesic benefit.\textsuperscript{23}

The fact that the totality of evidence in the perioperative period does not universally support IV over oral acetaminophen does not mean there is no role for IV acetaminophen.\textsuperscript{21} In patients who undergo lengthy surgery, have altered absorption in the perioperative period, or are strictly NPO (nothing by mouth) for an extended period postoperatively, IV acetaminophen is a useful analgesic adjunct and is preferable to opioids in many patient populations, such as those with obstructive sleep apnea or those with substance use disorder receiving opioid replacement therapy.

**Nonsteroidal Anti-Inflammatory Drugs**

NSAIDs are a well-established class of analgesics that can be very effective additions to multimodal protocols, especially for patients undergoing orthopedic surgery involving substantial inflammation. The primary mechanism of action of NSAIDs is inhibition of COX and prostaglandin synthesis.\textsuperscript{24}

A review that summarized the findings of 13 randomized controlled trials concluded that a single dose of ketorolac improves postoperative pain and reduces nausea and vomiting, although orthopedic surgery was not the focus.\textsuperscript{25} Another review found that the number needed to treat when combining ibuprofen 400 mg and paracetamol (acetaminophen) was 1.5 to achieve a 50% reduction in pain.\textsuperscript{26}

A frequently cited concern with NSAIDs is an increased postoperative bleeding risk, but evidence does not support this claim.\textsuperscript{16} In patients with preexisting chronic kidney disease, an appropriate level of caution is warranted.\textsuperscript{24} Additional concerns sometimes raised by surgeons are possible nonunion or poor bone healing in orthopedic patients exposed to NSAIDs, but available evidence does not support these concerns. A recent review found that the quality of the studies that reported impaired bone healing with NSAID use was much lower than the quality of the studies that concluded NSAIDs did not impair bone healing.\textsuperscript{27}

A review of the effects of NSAIDs on soft tissue healing in sports medicine surgery was unable to reach definitive conclusions but did state that NSAIDs may not affect healing rates following most procedures, except for celecoxib possibly inhibiting tendon-to-bone healing in rotator cuff repair surgery.\textsuperscript{28} For patients with a significant history of coronary artery disease, use of scheduled NSAIDs should be carefully considered. Avoiding high doses and limiting duration of NSAID therapy postoperatively have been recommended. Finally, in patients at risk for or who have a history of gastrointestinal ulcers, a COX-2 inhibitor such as celecoxib may be substituted for a nonselective NSAID to reduce this risk.\textsuperscript{29}

**Gabapentinoids**

Agents that fall into this class include gabapentin and pregabalin. Both are anticonvulsants and interact with voltage-gated calcium channels.\textsuperscript{31} There is evidence that gabapentin and pregabalin can help improve postoperative pain when included as part of a multimodal regimen, but there are some concerns about sedation.\textsuperscript{32,33} A review by Savelloni et al found that although patients who received gabapentinoids did not have more respiratory depression events than those who did not, the subset of patients who had undergone surgery were more likely to have had respiratory depression.\textsuperscript{34} This reinforces the need for increased vigilance in orthopedic patients and others who receive gabapentinoids and opioids together postoperatively. Our recommendation is to consider an age limit for using gabapentinoids or at least start with a lower dose (Table).

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

This class of analgesics includes ketamine and magnesium. Ketamine can be administered through various routes, including oral, intranasal, intramuscular and IV. Because the IV route is the most common in the perioperative setting, it will be the focus in this review.
National guidelines recently published by the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommend ketamine infusions for patients undergoing painful surgery and patients who are opioid tolerant. Despite inconsistent findings reported by reviews on perioperative ketamine and psychomimetic adverse drug effects (ADEs), which include hallucinations, nightmares and out-of-body experiences, caution should be exercised when using this drug, especially for patients undergoing ambulatory surgery. The risk–benefit ratio may not be favorable in this setting.

Clonidine and/or a benzodiazepine should be ordered to decrease the chance of severe ADEs, because patients who are not given an adjuvant appear to have the highest risk for experiencing ADEs. The analgesic benefit of a single intraoperative bolus of ketamine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Suggested Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Centrally acting analgesic; possible COX inhibition</td>
<td>≥50 kg: Preoperative: 1,000 mg PO or IV Intraoperative: 1,000 mg IV Postoperative: 1,000 mg q6h</td>
<td>Maximum recommended daily dose for patients ≥50 kg is 4 g</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>COX-2-selective inhibition</td>
<td>Preoperative: 400 mg PO Postoperative: 200 mg q12h</td>
<td>Increases risk for myocardial infarction</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Inhibition of voltage-gated calcium channels</td>
<td>Preoperative: 600-1,200 mg PO Postoperative: 300 mg PO q8h</td>
<td>Can cause sedation, especially in elderly</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>COX inhibition</td>
<td>Preoperative: 600-800 mg PO Postoperative: 600 mg q6h</td>
<td>Reduce dose in patients with reduced CrCl</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA antagonism</td>
<td>Intraoperative: bolus of 0.25-0.3 mg/kg IV, followed by infusion of 0.25 mg/kg per hour Postoperative: 0.25 mg/kg per hour</td>
<td>Most effective in surgery with moderate to severe pain</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>COX inhibition</td>
<td>Preoperative: 15-30 mg PO or IV Intraoperative: 15-30 mg IV Postoperative: 15-30 mg q6h</td>
<td>Intraoperative bolus alone likely of minimal benefit</td>
</tr>
<tr>
<td>Magnesium</td>
<td>NMDA antagonism</td>
<td>Intraoperative: bolus 30-50 mg/kg, followed by 8-10 mg/kg per hour infusion</td>
<td>Exercise caution in patients with gastrointestinal ulcers, acute or chronic kidney disease, or coagulopathy</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Inhibition of voltage-gated calcium channels</td>
<td>Preoperative: 150 mg PO Postoperative: 75 mg q12h PO</td>
<td>Can cause sedation, especially in elderly</td>
</tr>
</tbody>
</table>

COX, cyclooxygenase; CrCl, creatinine clearance; NMDA, N-methyl-D-aspartate; PO, oral

Based on references 5 and 62.
has been questioned recently in light of the PODCAST trial findings, which concluded that a bolus of ketamine did not reduce delirium or pain after surgery but did increase the incidence of hallucinations and nightmares in the elderly. In general, if ketamine is used intra- or postoperatively, an infusion is preferred to both maximize analgesia and minimize ADE risk.

Magnesium alone has shown inconsistent results as an analgesic but may have a synergistic effect when combined with morphine or ketamine. Studies have shown that it can reduce anesthetic and opioid requirements when given perioperatively with few if any side effects and may provide more stable hemodynamic parameters during surgery. Magnesium may be administered as an IV infusion before or after induction of anesthesia and may be a useful adjunct when combined with other components of a robust multimodal regimen.

**Local Anesthetics**

The use of local anesthetics in the form of peripheral nerve blocks and neuraxial blocks is a highly effective method for controlling pain after orthopedic surgery. Regional anesthesia has been shown to provide analgesia superior to systemic opioids in multiple surgery types, including total knee arthroplasty (TKA), shoulder surgery and foot/ankle surgery. In the setting of ambulatory surgery, regional anesthesia reduces nausea and vomiting and the time spent in the PACU.

In modern orthopedic surgery, peripheral nerve blocks may be more attractive than neuraxial blocks because they affect only the surgical extremity, are not associated with hypotension, and have better compatibility with anticoagulation. For TKA, peripheral nerve blocks provide effective analgesia, and newer techniques, such as the IPACK (interspace between the popliteal artery and posterior capsule of the knee) block, may help address posterior knee pain, which is not covered by other nerve blocks.

To extend the duration of blockade, adjuvants such as dexamethasone or dexmedetomidine may be added to the local anesthetic mix or given systemically, or a continuous catheter technique may be used. For practices where continuous peripheral nerve blocks are not practical, the addition of dexamethasone can prolong brachial plexus blocks and lower extremity blocks by several hours. If a continuous peripheral block program is feasible, it offers advantages in that analgesia may be prolonged beyond the duration possible with adjuvants, the dose and clinical effect are titratable, and additional bolus doses may be given via the catheter. Patients can be discharged home with ambulatory pumps attached to their peripheral nerve catheters, and these can be easily removed by patients or family members and discarded along with single-use pumps.

A recent study, however, suggests that a continuous adductor canal block does not offer many advantages over a single-injection block in terms of analgesic outcomes in all patients. However, before surgery it is impossible to know which patients will need prolonged regional analgesia. Although peripheral nerve blocks reduce short-term pain and are a valuable component of multimodal pathways, they have not yet been shown to reduce the risk for persistent opioid use.

Local anesthetics may also be given via the periarticular route. There may be advantages in combining periarticular local anesthetics with peripheral nerve blocks in TKA, including improved analgesic outcomes. Typically, surgeons will inject a local anesthetic “cocktail” during incision closure at the end of TKA. These cocktails contain a local anesthetic plus a variety of medications, which may include opioids, NSAIDs, corticosteroids and epinephrine. The “best” combination remains unknown.

Reviews have shown significant variability in the components of periarticular injections for TKA. One recent meta-analysis concluded that pain, opioid consumption, and nausea and vomiting are reduced with the combination of adductor canal block and periarticular injections for TKA, and another reported that earlier ambulation was accomplished more frequently with the combination than with periarticular injections alone.

The choice among peripheral nerve blocks alone, periarticular injections alone or the combination should be made based on institutional and clinician preferences that factor in the patient population, surgical techniques, workflow, staffing and resources at each location.

Intravenous lidocaine infusions are another option for incorporating local anesthetics into perioperative multimodal regimens. Lidocaine infusions improve analgesia after spine surgery, but there is conflicting evidence about its overall benefits as a perioperative analgesic, with a meta-analysis concluding that lidocaine infusions do not reduce perioperative pain but may decrease the risk for persistent postsurgical pain. Lidocaine infusions may exert their analgesic effects through a reduction in inflammatory mediators, which has been shown to occur when given intraoperatively. It should be considered if regional anesthesia or periarticular injections are not desired, unavailable, or contraindicated.

**Opioids**

Many clinicians have favored opioids over the years, an observation that is likely related to their ease of use, availability, predictability and familiarity. This preference has recently come under scrutiny as national attention has focused on the role of prescription opioids in the current drug crisis. We believe that opioids should be reserved for severe pain that is not relieved by any other modality and only after alternatives have been tried and failed or are incompletely effective. This concept is not new and was the basis of the World Health Organization’s analgesic ladder that was proposed in 1986, and emphasized nonopioids as the foundation of analgesia.

Commonly prescribed perioperative oral opioids include oxycodone, hydrocodone and tramadol. A
common misconception is that tramadol is not an opioid and that it is less addictive than other opioids. A recent report from the CDC highlighted the association between tramadol prescriptions and long-term opioid use. A brief course of a short-acting opioid is generally the safest strategy. Patients whose analgesic requests are outliers should be examined closely to determine the underlying reasons for their requests for additional opioid.

References

Conclusion
Multimodal analgesia can improve outcomes in many different surgical settings and should be the standard for orthopedic surgery. Drug shortages have forced anesthesiologists to expand their knowledge and clinical experience to include agents that have not been traditionally used, and so perioperative plans must be designed with flexibility. The importance of multimodal analgesia that minimizes opioid use and emphasizes nonopioids has never been greater than during the current opioid epidemic and in light of emerging evidence that even brief perioperative opioid exposures can increase the risk for long-term opioid use.


