Special
REPORT

Multimodal Management Of Acute Pain: The Role of IV NSAIDs

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Acute pain is common in hospitalized patients, particularly in postoperative patients. In fact, postoperative pain often is undertreated and is associated with poor outcomes, higher costs of care, poor patient satisfaction, and an increased risk for developing chronic pain syndromes. The failure to treat postoperative pain adequately is at least in part due to the reliance on monotherapy with opioid analgesics.[1] Fortunately, the increasing use of multimodal analgesia is resulting in improved pain control for postoperative patients.

This monograph discusses the concept of multimodal analgesia and preemptive analgesia and presents new data concerning IV nonsteroidal anti-inflammatory drugs (NSAIDs) and how they can be used to treat acute pain effectively in hospitalized patients.

Prevalence and Severity of Acute Pain In Hospitalized Patients

Acute pain in hospitalized patients is most commonly related to surgical procedures. With more than 45 million nonambulatory surgeries being performed annually in the United States,[2] this translates into a high absolute number of patients affected. Despite advances in pain medicine, including IV and epidural patient-controlled analgesia, pain management continues to pose a challenge for clinicians.

Several studies have investigated the epidemiology of acute pain in postoperative patients. For example, Apfelbaum and colleagues conducted telephone surveys with a random sample of 250 adults who had undergone surgical procedures recently in the United States.[1] Survey questions focused on the severity of postsurgical pain, education received, treatment, satisfaction with pain medication, and overall perceptions about postoperative pain and treatment.[1] The researchers reported that approximately 80% of patients experienced acute pain after surgery, and of these patients, 86% had moderate, severe, or extreme pain.[1] Additionally, experiencing postoperative pain was the most common concern (59%) of patients before surgery, and these concerns even caused some patients to postpone surgery.[1]

Warfield and Kahn reported similar results in a study using telephone questionnaire surveys of patients who had undergone surgery in teaching or community hospitals.[3]

Again, approximately 77% of patients reported experiencing pain after surgery, and 80% of these patients rated pain after surgery as moderate to extreme.[3]

Other studies suggest that pain can persist for several days following surgery. Lynch and colleagues assessed pain after elective noncardiac surgery through the use of questionnaires and a 10-cm visual analog scale in 276 patients.[4] They reported that the mean maximum pain score on postoperative day 1 was 6.3 (moderate pain) and decreased only slightly to 5.6 by postoperative day 3.[4] Furthermore, using a questionnaire survey, Beauregard and colleagues assessed pain in 89 patients undergoing ambulatory surgery and found that 40% reported moderate to severe pain during the first 24 hours after discharge; pain decreased over time but was severe enough to interfere with daily activities, even several days after surgery.[5]

Consequences of Acute Postoperative Pain in Hospitalized Patients

Inadequate pain management can have profound and long-lasting implications. Ischemic events are well documented in patients following surgery and are thought to be indicative of the risk for postoperative morbidity, including serious arrhythmia, myocardial infarction, congestive heart failure, intracranial hemorrhage, and death.[6,7] The stresses of surgery and postoperative stress are thought to be contributing factors to ischemic events. Inadequate pain management is a major trigger of the sympathetic nervous system and therefore is viewed as a strong contributor to postoperative stress.[6] Beattie followed 55 patients with 2 or more risk factors for ischemia (coronary artery disease, high blood pressure, history of myocardial infarction, etc) for 24 hours following noncardiac surgery.[6] His results indicate stress as a contributing factor to the early ischemic events observed in this study because tachycardia often was observed along with ischemia.

Other short-term consequences of acute pain include splinting, which can lead to atelectasis and pneumonia,[8] as well as delayed mobilization,[9] which can increase the risk for deep venous thrombosis and subsequent pulmonary embolism.[10,11]

Table 1. Adverse Effects Associated With Opioid Monotherapy for Postoperative Pain

Allergic reactions
Gastrointestinal effects
Hypotension
Nausea/vomiting
Respiratory depression/failure
Sedation, confusion
Urinary retention
Based on Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother.* 2007;41(3):400-406.

The psychological effects of uncontrolled pain, including insomnia, depression, and anxiety, also may contribute to poor patient outcomes and decreased patient satisfaction.[12]

A frequently unrecognized risk associated with undertreatment of acute postoperative pain is the potential to develop chronic pain syndromes.[13] In fact, Perkins reported that postoperative pain was the main predictor for development of chronic pain syndromes and that improved postoperative analgesia reduced the incidence of this complication.[13]

Poorly managed postoperative pain also results in increased resource utilization and health care costs. For example, Morrison and colleagues studied 411 patients undergoing surgical repair of a hip fracture and reported that patients with higher postoperative pain scores had significantly longer hospital length of stay, were significantly less likely to be ambulating by day 3, took significantly longer to move past a bedside chair, and had lower locomotion scores at 6 months.[9] Furthermore, Coley and colleagues reported that postoperative pain was the most frequent reason for hospital readmission after discharge.[14]

Management of Acute Pain In Hospitalized Patients

Opioid monotherapy remains a widely used mode of postoperative analgesia.[15] Opioids are potent analgesics and are available in a wide variety of formulations, including IV, oral, and transdermal, which is useful in the postoperative setting as well as for medication transitions at time of hospital discharge. Although monotherapy with these agents can be effective in some cases, opioids have various idiosyncratic or dose-limiting side effects that curtail their practical efficacy as well as expose patients to dangerous adverse events (AEs).[15,16] The central nervous system (CNS) effects (eg, sedation, somnolence, respiratory depression) associated with opioids are particularly dangerous and increase the risk for aspiration, respiratory failure, decreased mobility, and falls (Table 1).[15,16] Other AEs are common even at low doses of opioids and include constipation and ileus, which can result in significant discomfort, longer hospital stays, and nausea and vomiting, which can lead to wound dehiscence and delayed recovery.[15,16] Because opioid-induced nausea and vomiting is dose-dependent, a reduction in opioid burden while maintaining optimal pain relief offers clinical benefits.[17]

The limitations of opioid monotherapy combined with the evidence of undertreatment of postoperative pain have led several medical societies and quality assurance groups to issue guidelines and launch initiatives to improve the management of postoperative pain. As part of a comprehensive initiative, the Agency for Health Care Policy and Research issued guidelines for acute pain management in 1992.[18] The guidelines promote aggressive treatment of acute pain and educate patients about the need to communicate unrelieved pain. In 2004, the American Society of Anesthesiologists released an update to its 1994 guidelines for acute pain management in the perioperative setting.[19] These guidelines promote standardization of procedures and the use of epidurals and patient-controlled analgesia pumps.[19] They also recommend that proactive planning—including obtaining pain history and preoperative, intraoperative, and postoperative pain treatment—be a part of the institution's interdisciplinary care plan.[19] More recent initiatives
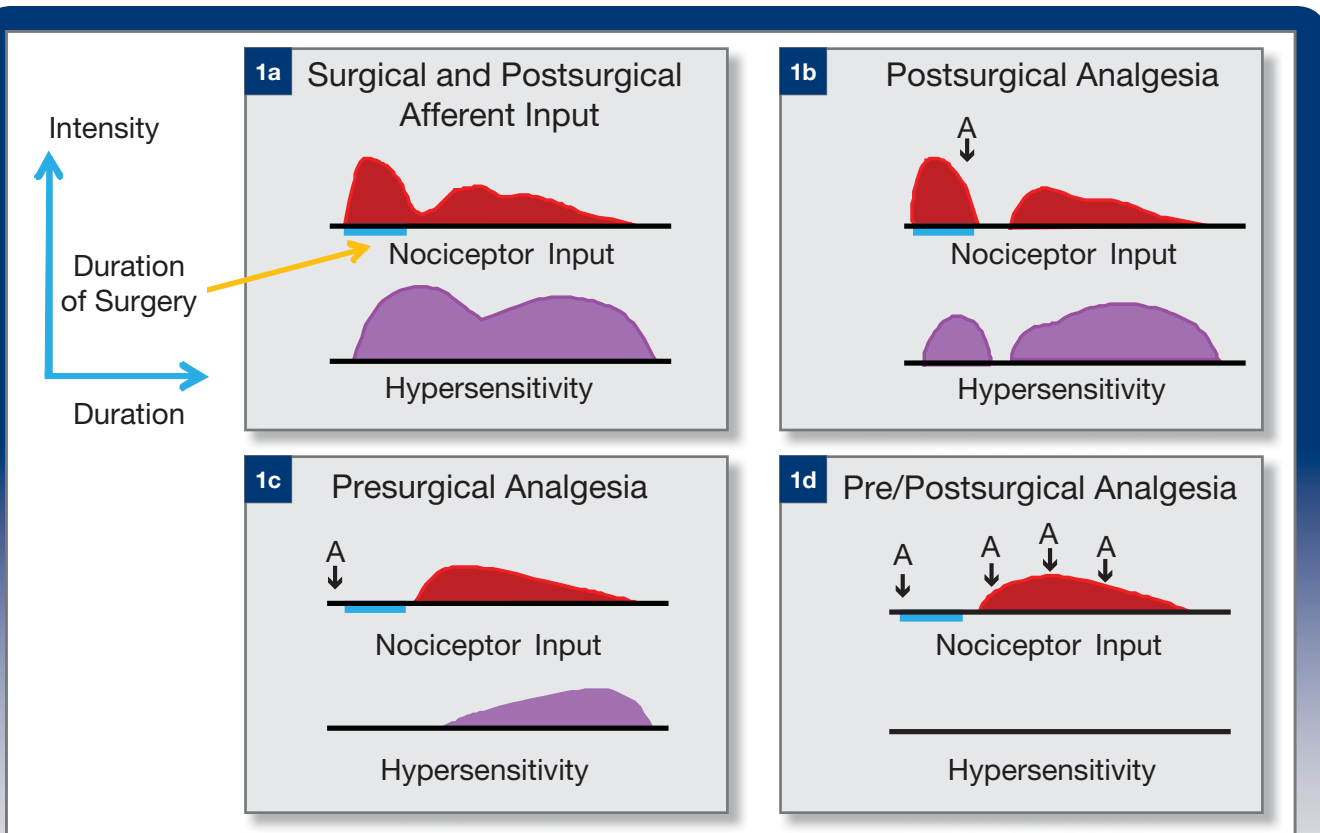
Figure 1. Preemptive analgesia may reduce wound hypersensitivity.

Several perioperative analgesic dosing regimens and their effect on nociceptor activity and wound site hypersensitivity.

Figure 1a: The non-treatment regimen, in which a patient receives no analgesic intervention and subsequently develops high-grade hypersensitivity.

Figure 1b: The analgesic is administered postsurgically after central sensitization has already occurred. This reduces pain intensity for a short time. However, it has no long-term effect on the development or magnitude of hypersensitivity.

Figure 1c: Preoperative administration of the analgesic decreases both nociceptor input and the magnitude of hypersensitivity.

Figure 1d: The preoperative dose of the analgesic is followed by additional doses administered at regular intervals during postsurgical recovery. This is the most effective regimen for prevention of central sensitization and wound site hypersensitivity.

A, analgesia

Adapted with permission from Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Physician.* 2001;63(10):1979-1984, and Woolf CK, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg.* 1993;77(2):362-367.

to improve management of postoperative pain cite the potential efficacy of multimodal analgesia and preemptive analgesia.[19]

Multimodal Analgesia

Multimodal analgesia is defined as the simultaneous use of different classes or modes of analgesics that modulate different pathways and receptors in order to provide superior pain control. Multimodal analgesia provides several types of benefits to postoperative patients.[12,20-22] First, use of agents with different analgesic mechanisms can result in synergistic effects and thereby produce greater efficacy.[21] Second, the synergism between these agents allows use of lower doses of each respective agent, thereby limiting dose-related AEs, particularly when these regimens allow for lower doses of opioids.[12,22] These actions, in turn, may facilitate earlier mobilization and rehabilitation after surgery, earlier transition to the outpatient setting, and decreased costs of care.[12]

Modern multimodal analgesia consists of the use of systemic and local pharmacologic agents as well as regional anesthesia and perineural blockade.[12,21,22] Ideal components of pharmacologic multimodal analgesia include those agents with potency for modulating one or more discrete mechanisms of pain transmission and those agents that possess a good safety profile (eg, minimal bleeding risk).[12,22] Furthermore, the availability of an analgesic in an IV formulation is critical in the immediate postoperative period for various reasons, including improved bioavailability and earlier onset of analgesic effect, and because these patients may experience postoperative nausea and vomiting.[21] It is also beneficial because the enteral route may be compromised by the nature of the surgery, thereby precluding oral drug administration.[22] Among IV agents used in multimodal analgesia are the opioids, NSAIDs, acetaminophen, α_2-agonists (eg, clonidine), and N-methyl-D-aspartate receptor antagonists (eg, ketamine).[12,20,21]

Preemptive Analgesia

An additional pain management strategy, originally proposed more than 20 years ago, is preemptive analgesia. This requires a comprehensive understanding of the mechanism of pain transmission and the subsequent adaptive or maladaptive responses of the nervous system.[23]

The peripheral nervous system and the CNS are essential in perceiving pain.[24-26] Peripheral nociceptors play an important role in translating noxious stimuli by sending signals along myelinated A and unmyelinated C fibers in the dorsal root ganglion.[24] Synapses occur between the axons in the dorsal horn of the spinal cord and send signals along the spinothalamic tract of the spinal cord to the brain.[24]

Noxious stimuli that are sufficiently intense to produce tissue injury, as occurs during surgery, characteristically generate prolonged post-stimulus sensory disturbances that include continuing pain, an increased sensitivity to noxious stimuli, and pain following innocuous stimuli.[12,25,26] This may result from either a reduction in the thresholds of skin nociceptors (peripheral sensitization) or an increase in the excitability of the CNS (central sensitization), which can cause exaggerated responses to stimuli (Figure 1).[24-26]

Based on these observations, investigators have studied and reported good efficacy for preemptive administration of analgesics to block transmission of noxious stimuli and thereby preclude the cascade of events that leads to peripheral and central sensitization.[25-27] This preemptive strategy results in improved pain control in the postoperative context and related improvements in a variety of outcome measures.[26,27]

Pluripotent Effects of IV NSAIDs for Postoperative Pain Control

NSAIDs have been used for the treatment of pain for decades, and investigators increasingly are recognizing the particular utility of these agents for improved control of postoperative pain. The primary mechanism by which NSAIDs exert their effects is via inhibition of the arachidonic acid–cyclooxygenase (COX) pathways.[28] This cascade consists of 2 distinct pathways mediated through COX-1 and COX-2.[28] Although the detrimental effects of some NSAIDs (eg, renal dysfunction, gastrointestinal [GI] mucosal compromise, platelet inhibition) are mediated by inhibition of the COX-1 pathway, the analgesic effect and anti-inflammatory effects are attributable primarily to inhibition of COX-2.[28-30] This is consistent with experimental evidence showing that prostaglandin E2 (PGE_2), which is generated by the COX-2 pathways, plays a critical role in the induction of both peripheral and central sensitization.[31-34] Thus, the specificity of certain NSAIDs for the different COX enzymes has significant implications in terms of clinically analgesic potency as well as the probability of AEs.

NSAIDs modulate pain pathways in multiple ways.[35] NSAIDs reduce inflammatory hyperalgesia and allodynia by reducing prostaglandin synthesis; they can decrease the recruitment of leukocytes and consequently their derived inflammatory mediators; and they cross the blood–brain barrier to prevent prostaglandins (ie, pain-producing neuromodulators) in the spinal cord.[36] In this manner, NSAIDs reduce local inflammation and may prevent both peripheral and central sensitization (Figure 2).[36] Opioids do not modulate PGE_2 or inflammatory pathways, whereas acetaminophen acts centrally but does not act at peripheral sites.[37] Additionally, IV NSAIDs can act as
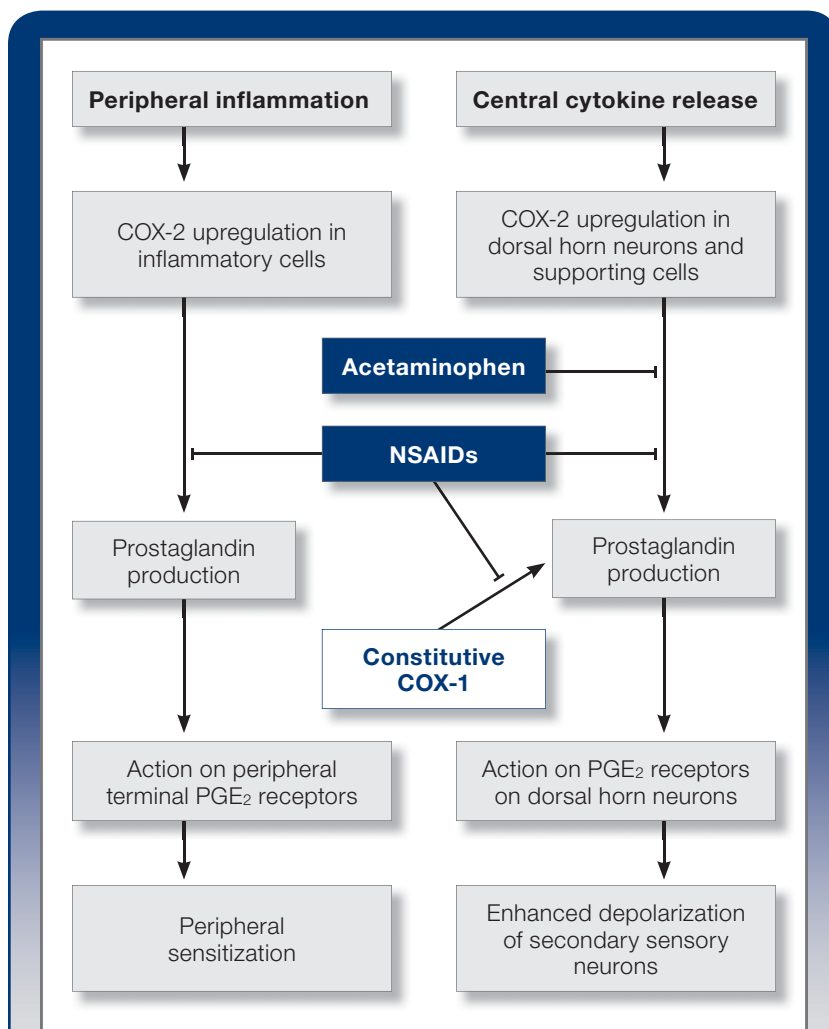

Figure 2. Mechanism of analgesic action of cyclooxygenase inhibitors.

COX, cyclooxygenase; **NSAID,** nonsteroidal anti-inflammatory drug; **PGE_2,** prostaglandin E2

Adapted from Golan DE. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy.* 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2008.

Table 2. Properties of Parenteral NSAIDs		
	Ketorolac (Toradol®)	**Ibuprofen (Caldolor®)**
Indications	Management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting	Management of mild to moderate pain Management of moderate to severe pain as an adjunct to opioid analgesics Reduction of fever
Dosing	15-30 mg IV every 6 h as necessary	Pain: 400-800 mg IV over 30 min every 6 h as necessary Fever: 400 mg IV over 30 min, followed by 400 mg every 4-6 h or 100-200 mg every 4 h as necessary
Half-life	5-6 h (racemic mixture)	2.22 h (400 mg) 2.44 h (800 mg)
Duration listed in label	No more than 5 d	Unrestricted
Black Box Warnings	Can cause peptic ulcers, GI bleeding, and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Therefore, it is contraindicated in patients with active peptic ulcer disease, in patients with recent GI bleeding or perforation, and in patients with a history of peptic ulcer disease or GI bleeding. Elderly patients are at greater risk for serious GI events May cause an increased risk for serious CV thrombotic events, MI, and stroke, which can be fatal. This risk may increase with duration of use. Patients with CVD or risk factors for CVD may be at greater risk. It is contraindicated for the treatment of perioperative pain in the setting of CABG surgery Contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion Ketorolac inhibits platelet function and is therefore contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis or incomplete hemostasis, and those at high risk for bleeding. It is contraindicated as prophylactic analgesic before any major surgery Contraindicated in labor and delivery and nursing mothers, and in patients currently receiving aspirin or other NSAIDs	NSAIDs may increase the risk for serious CV thrombotic events, MI, and stroke, which can be fatal. Risk may increase with duration of use. Caldolor is contraindicated for the treatment of perioperative pain in the setting of CABG surgery NSAIDs increase the risk for serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Events can occur at any time without warning symptoms. Elderly patients are at greater risk

CABG, coronary artery bypass graft; **CV,** cardiovascular; **CVD,** cardiovascular disease; **GI,** gastrointestinal; **MI,** myocardial infarction; **IV,** intravenous; **NSAID,** nonsteroidal anti-inflammatory drug

Based on Toradol prescribing information. http://www.drugs.com/pro/ketorolac-tromethamine.html, and Intravenous ibuprofen (Caldolor®) prescribing information. http://www.caldolor.com/pdfs/Caldolor_Full_Prescribing_Information.pdf.

adjunct regional blockade by inhibiting PGE and cytokines in addition to suppressing neural responses to noxious injury.[35]

There are currently 2 parenteral NSAIDs that are approved for use in the United States: IV ketorolac and IV ibuprofen (Table 2).[38,39]

IV Ketorolac (Toradol®)

Ketorolac tromethamine is an IV NSAID formulation that was approved for use by the FDA in 1989.[40] It is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting.[38] Numerous studies have documented the efficacy of postoperative use of IV ketorolac for the reduction of pain, reduction of opioid use, and facilitation of quicker recovery and rehabilitation.[41,42]

Of note, ketorolac has much more potent effect on COX-1 than on COX-2. This has important implications for clinical use.[29] The negative effect of NSAIDs on renal function, GI

Reduction in Pain Intensity Scores After Orthopedic Surgery

Assessed at Rest
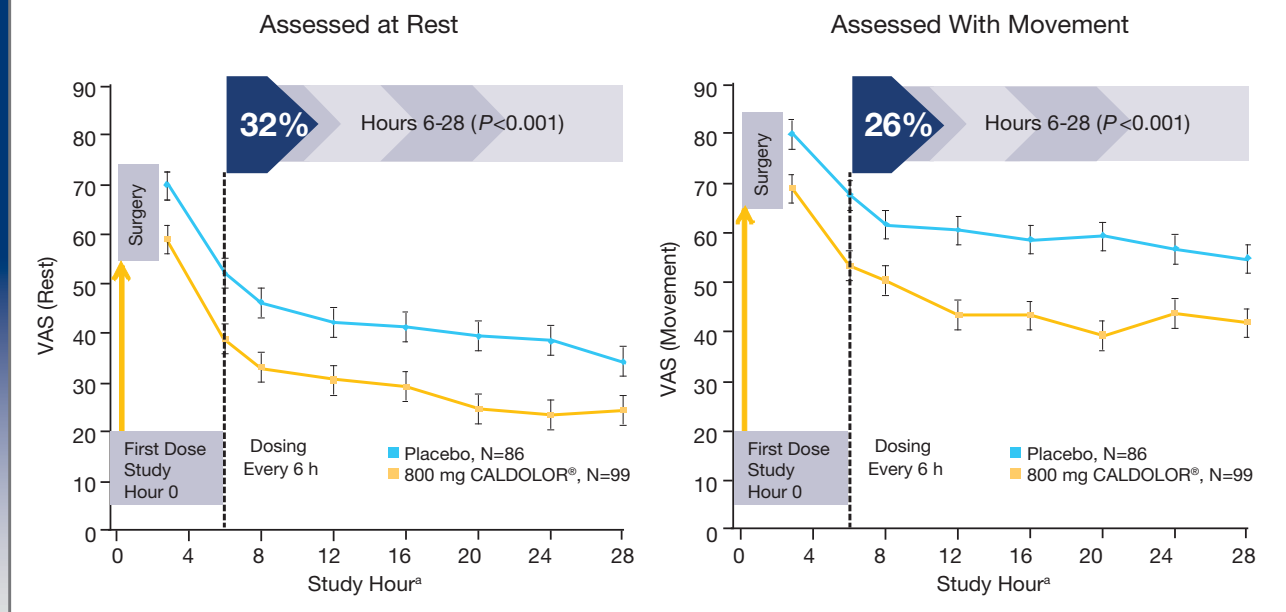

Assessed With Movement

Figure 3. Orthopedic pain study: VAS scores at rest and with movement.

In this study, patients woke up in less pain and remained in less pain throughout the postoperative period whether assessed at rest or with movement.

VAS, visual analog scale

[a] Statistical significance was demonstrated at each assessment point.

Based on Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind placebo-controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in post-operative orthopedic adult patients. *Pain Med.* 2010;11(8):1284-1293.

mucosa, and platelet function are mediated primarily through the COX-1 pathways.[28,29] Thus, IV ketorolac is contraindicated in patients with renal insufficiency (which is particularly prevalent in elderly populations) or a history of GI ulcers or bleeding disorders.[38] These effects are primary determinants indicating short-term use only.[38]

Ketorolac has a high degree of COX-1 selectivity of NSAIDs used for acute pain management.[29] The potent effect of ketorolac on COX-1 also may result in platelet dysfunction, which can increase the risk for bleeding in the perioperative setting.[38] Indeed, postoperative hematomas and other signs of wound bleeding have occurred in association with the perioperative use of IV ketorolac.[38] As such, the prescribing information for IV ketorolac contains a Black Box Warning against its use as a prophylactic analgesic before any major surgery.[38]

Despite contraindication, IV ketorolac has been studied as a prophylactic analgesic with varying results. Cabell and colleagues performed a randomized, double-blind trial of preemptive ketorolac in patients undergoing laparoscopic ambulatory surgery and reported that these patients actually had higher postoperative pain scores and greater narcotic use.[43] Similarly, Vanlersberghe and colleagues conducted a randomized, double-blind, placebo-controlled trial of preemptive ketorolac in patients undergoing orthopedic surgery and reported that there was no difference in postoperative pain

scores or morphine use when comparing those who received ketorolac and those who did not.[44] Yet, as demonstrated by El-Tahan and colleagues in a randomized, double-blind, placebo-controlled study assessing hemodynamic and hormonal effects in managing pain following cesarean delivery, preemptive use of ketorolac has optimized postoperative analgesia.[45]

IV Ibuprofen (Caldolor®)

A formulation of IV ibuprofen (Caldolor®) was approved for use in the United States in June 2009, and it is indicated for management of mild to moderate pain, management of moderate to severe pain as an adjunct to opioid analgesics, and reduction of fever.[39] Similar to oral ibuprofen, the IV formulation can inhibit both COX-1 and COX-2.[39] IV ibuprofen has more "balanced" affinity for the COX isoenzymes.[29,39] In key clinical trials, bleeding, gastric, and renal events were similar to placebo.[39] This has significant implications for the clinical use of IV ibuprofen.[39,46]

The efficacy and safety of IV ibuprofen was studied by Southworth and colleagues, who conducted a multicenter, randomized, double-blind, placebo-controlled dose-ranging study to assess the effects of IV ibuprofen or placebo in 406 patients undergoing orthopedic or abdominal surgery.[47] Ibuprofen was given at 400 or 800 mg or placebo doses every 6 hours beginning at the initiation of wound closure and continued for 48

hours.[47] After that period, additional ibuprofen dosing was available as necessary.[47] Patients in all 3 groups had access to morphine throughout the study.[47]

IV ibuprofen at a dose of 800 mg was associated with reduced morphine use during the first 24 hours (by 22% vs placebo; $P=0.030$) and significant reductions in pain at rest (30.6% reduction at 24 hours vs placebo; $P<0.001$) and with movement (18% reduction at 24 hours vs placebo).[47] Additionally, IV ibuprofen at a dose of 400 mg was associated with a nonsignificant reduction in narcotic use and significant reductions in pain at rest and with movement when compared with placebo.[47] IV ibuprofen reduced the incidence of fever when compared with placebo and was not associated with significant increases in AEs, including bleeding and renal toxicities, with the exception of an increased incidence of dizziness with the 800-mg dose.[47] Interestingly, there were significant reductions in the proportions of patients who experienced GI disorders, such as nausea or constipation, in the 400- and 800-mg IV ibuprofen groups compared with the placebo group (74% and 71%, respectively, vs 84%; $P=0.05$ and $P=0.009$).[47]

Another Phase III multicenter, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of IV ibuprofen (800 mg every 6 hours beginning at the initiation of wound closure, continued for 8 doses, and then as needed every 6 hours for up to 5 days following surgery) compared with placebo as a postoperative analgesic in 319 patients undergoing elective abdominal hysterectomy.[48] IV ibuprofen was associated with a reduction in morphine requirements over the first 24 hours (by 19% vs placebo; $P<0.001$) and resulted in a significant reduction in pain at rest (21% reduction at 24 hours vs placebo; $P=0.011$) and with movement (14% reduction at 24 hours vs placebo; $P=0.010$).[48] Time to ambulation also was significantly faster in the IV ibuprofen-treated group than in the placebo group (23.4 vs 25.3 hours; $P=0.009$).[48] As with the dose-ranging study, there was no difference in treatment-emergent AEs, including nausea and flatulence, between the study groups.[48]

Perhaps a more optimal way to administer NSAIDs for postoperative pain is to provide therapeutic doses prior to surgical dissection and tissue upregulation of COX-2. Singla and colleagues also investigated the efficacy of IV ibuprofen as a preemptive analgesic.[46] This was a multicenter, randomized, double-blind, placebo-controlled trial of IV ibuprofen versus placebo in 185 adult patients undergoing elective orthopedic surgery.[46] Patients were randomized to receive either 800 mg IV ibuprofen or placebo, beginning at induction and then given every 6 hours for 5 doses and then as needed every 6 hours for up to 5 days following surgery.[46] IV ibuprofen was associated with a reduction in morphine requirements in the postoperative period (by 31% vs placebo; $P<0.001$).[46] During this time period, IV ibuprofen also was associated with a significant reduction in pain at rest (32% vs placebo; $P<0.001$) and pain with movement (26% vs placebo; $P<0.001$) (Figure 3).[46] Importantly, there was no difference in bleeding, renal toxicity, or other AEs between the study groups.[46]

Conclusion

The prevalence of acute pain is high in hospitalized patients, particularly in postoperative patients, and poorly controlled pain is associated with medical complications, poor patient satisfaction, impaired rehabilitation, delayed hospital discharge, and an increased risk for developing chronic pain. Furthermore, pain often is undermanaged, at least in part because of the limitations of opioid monotherapy.

Optimal pain relief may require a multimodal approach and possibly preemptive analgesia. IV NSAIDs address multiple mechanisms of pain and can be used in the multimodal management of postoperative acute pain. IV ketorolac is only indicated for short-term therapy and is contraindicated for use as a preemptive analgesic. By contrast, IV ibuprofen is effective for use as both a preemptive analgesic and a postoperative analgesic without an increased risk for AEs and without restrictions for duration of use. These data suggest that IV ibuprofen is well suited for use in multimodal and preemptive analgesia in hospitalized patients with acute pain.

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