Cyclooxygenase-2–selective inhibitors in the management of acute and perioperative pain

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ABSTRACT

Postsurgical pain is often undertreated. Opioids are frequently used in perioperative analgesia, but concern about side effects can result in administration of an inadequate dose for pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used increasingly for postoperative analgesia. The use of balanced analgesia—a combination of opioids, NSAIDs, and local anesthesia utilizing agents from other classes (eg, ketamine, clonidine)—improves the efficacy of pain relief and decreases risk of side effects. While lacking some of the troublesome side effects of opioids, nonselective NSAIDs may cause bleeding as a result of their inhibitory effects on COX-1. For this reason, COX-2–selective inhibitors (coxibs) are attractive opioid-sparing analgesic options in the perioperative setting. Factors in addition to side effects such as time to onset of action, duration of action, maximum pain relief, use of rescue medication, and other factors relevant to a given pain model are important in determining overall analgesic efficacy. Clinical studies show that COX-2–selective inhibitors are effective for the treatment of preoperative and postoperative pain and reduce postsurgical requirements for opioids. This evidence supports a role for COX-2–derived prostaglandins as key mediators of nociceptive pain and peripheral sensitization (hyperalgesia). Pain management in the perioperative setting and the role of COX-2–selective inhibitors in acute and postoperative pain are reviewed here.

Understanding pain is central to the goals of medicine as pain may be both a cardinal manifestation of disease and a cause of suffering. Strategies of pain management have evolved to include an appreciation that pain is composed of physiologic as well as psychologic dimensions. Current concepts in pain management recognize the sensory perception of pain (nociception) as the progenitor of the psychic experience of pain, which can lead to suffering.[1] In chronic pain, there may be no discernible pathologic basis for pain, making syndromes like low-back pain and fibromyalgia difficult to understand and treat.[2,3] The importance of pain management to the care of patients is underscored by the fact that pain is now likened to a "fifth vital sign."

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standard for management of pain stresses the adverse physiolog-

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ic and psychologic burden of unrelieved pain.[4] The main tenets of the JCAHO standard are: continuous pain assessment—specially tailored assessments for special populations (ie, the elderly, people with AIDS or cancer, children); education about pain and pain management for patients and providers; and thorough ongoing documentation of reported pain as well as pharmacologic and nonpharmacologic interventions.[4]

Clinicians frequently cite several barriers to providing ample pain treatment. Among these are the safety and efficacy of analgesics. For opioid analgesics, several concerns exist, some more supported by clinical evidence than others, including serious side effects, the development of tolerance, and regulatory considerations. Such concerns may lead to the curtailed use of opioids in chronic pain.[5] However, concern for dependence may be exaggerated.[6] Increased education is needed in order that clinicians avail themselves of advances in diagnosis and pharmacologic management of pain.[5]

UNMET NEED IN PAIN MANAGEMENT

The clinical significance of pain may be said to lie fundamentally in its undertreatment.[5,7–9] As much as 10% to 20% of the adult population of the United States suffers from chronic pain, which is often inadequately treated and debilitating.[3] In the large Outpatient Pain Needs Assessment Survey (1990–1991), 42% of respondents reported they experienced cancer pain that was undertreated with inadequate analgesia.[7] Elderly persons are more likely to suffer from pain—especially chronic pain—and are more likely to be undertreated.[10] An extensive study of nursing home residents' nonmalignant pain, and impact of pain on their functional status and psychologic well-being, found, briefly, that of the 26.3% who experienced daily pain, 25% received *no* form of analgesia.[11]

It is estimated that over 31 million people in the United States each year undergo painful surgical and nonsurgical operative procedures, half of which may be inadequately treated for pain.[9,12] Undertreatment of pain has broad clinical implications and has been correlated with poor surgical outcomes such as delayed return to respiratory, bowel, and gastric function after surgery, immune suppression, and development of chronic pain.

A study of acute pain management in the postoperative setting showed that 77% of adults experienced inadequately treated pain after surgery: 71% still experienced pain even after being administered medication, and most of these (80%) described the pain as moderate to extreme.[13]

The Agency for Healthcare Policy and Research (AHCPR) and, more recently, the American Society of Anesthesiologists, published guidelines for the management of acute pain in the perioperative setting.[14,15] The major goals of these guidelines are to facilitate the efficacious and safe use of perioperative analgesia while reducing the severity of postoperative pain. The guidelines stress the importance of being proactive in planning analgesia and having patients and families involved in pain management. Education of patients and healthcare providers is needed to encourage optimal and safe use of analgesics. While authoritative guidelines are available, considerable effort is needed in their implementation. A study in 1995 found that only 46% of the hospitals surveyed had acute pain management programs or written guidelines, though an additional 22% planned to implement a pain management program in the near future.[13]

PATHOPHYSIOLOGY OF PAIN

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[5] *Nociceptive pain* is transiently invoked when pain-sensitive neurons (nociceptors) are activated by noxious stimuli (eg, physical, chemical, thermal). This pain is a protective response to adverse stimuli and subsides with removal of the stimulus. Nociceptive pain may initiate a phase of persistent acute pain triggered by tissue damage; the cellular and neuronal release of inflammatory mediators, such as prostaglandins, is involved.[16] Uncontrolled pain here increases patients' sensitivity.[8] Prolonged tissue damage and inflammation sensitizes nociceptors, resulting in a decreased pain threshold and protracted response (frequency of neuronal firing), or, *hyperalgesia*. Like nociceptive pain, hyperalgesia is linked to an adverse stimulus and diminishes with healing and decreased inflammation. Prolonged acute pain and hyperalgesia, however, can evolve into *chronic pain*.[16]

In contrast to acute pain, chronic pain is not a protective response and is no longer linked to a stimulus.[3] Progressive and prolonged stimulation of pain causes increased excitation of neurons in the

dorsal horn of the spinal cord.[5] This phenomenon is sometimes referred to as "wind-up pain." Once established, this abnormal condition continues independently of the initial cause (stimulus) and, for that reason, is considered pathologic pain.[17] Acute pain and hyperalgesia, which take place in the peripheral nervous system can, therefore, be distinguished from chronic pain, which takes place in the central nervous system. Mechanisms maintaining chronic pain are poorly understood.

The role of COX-2 in pain

Management of resolvable pain (eg, postsurgical pain) has benefited from advancements in understanding of the biochemical and molecular basis of pain. In injured tissue, acute pain is evoked locally, being mediated by released cellular components of the inflammatory process. Prominent among these are products of the cyclooxygenase (COX)-2 enzyme, in particular prostaglandin E_2 (PGE_2) and prostacyclin.[3] PGE_2 signals pain input by binding to receptors that regulate the calcium and sodium channels of nociceptive neurons.[18] PGE_2 can activate neurons or increase their sensitivity to pain. Following tissue injury, nociceptive fibers themselves are neuroeffective, as stimulated fibers release polypeptide mediators such as substance P, which enhances prostaglandin production.[6]

Inflammation in the periphery also generates pain hypersensitivity in adjacent tissues (*secondary hyperalgesia*) caused by spinal sensitization and a syndrome of muscle and joint pain, fever, lethargy, and anorexia.[19,20] Therefore, the effects of acute pain are inexorably linked to secondary events resulting from the widespread induction of COX-2 expression and subsequent production of prostaglandins in the spinal cord and brain. Inhibiting central COX-2 activity greatly reduces inflammatory pain hypersensitivity. The role of COX-2 in peripheral and central pain is the rationale for the use of COX-2-selective inhibitors to treat pain and its accompanying syndromes.[21]

TABLE 1
DRUGS USED IN RELIEF OF PAIN

- **Opioid analgesics**
  - Codeine
  - Oxycodone
  - Morphine
  - Hydromorphone
  - Levorphanol
  - Methadone
  - Meperidine
  - Butorphanol
  - Fentanyl
  - Tramadol
- **Nonopioid analgesics**
  - Nonselective NSAIDs
    - Aspirin
    - Ibuprofen
    - Naproxen
    - Fenoprofen
    - Indomethacin
    - Ketorolac (parenteral)
  - COX-2–selective inhibitors
    - Rofecoxib
    - Celecoxib
    - Valdecoxib
  - Others
    - Acetaminophen
    - Clonidine
    - Ketamine
- **Antidepressants**
  - Doxepin
  - Amitriptyline
  - Imipramine
  - Nortriptyline
  - Desipramine
  - Venlafaxine
- **Anticonvulsants**
  - Phenytoin
  - Carbamazepine
  - Gabapentin
- **Topical agents**
  - Capsaicin
  - Bupivacaine

■ OPTIONS FOR PAIN TREATMENT

Opioid analgesics

Pain medications may be broadly divided into two major categories: opioids and nonopioids (**Table 1**). Despite significant side effects, opioid analgesics remain the most potent and widely used pain-relieving drugs.[6]

These agents bind to opioid receptors where, acting as agonists, they inhibit pain-transmitting neurons and stimulate pain-inhibitory neurons. The μ- and Δ-opioid types of receptors are most commonly associated with pain relief.[16] Opioids are typically thought of as acting centrally, but peripheral opioid receptors are present in humans. The identification of such receptors may help explain the analgesic effect of some opioids. Intra-articular morphine, for example, has a significant analgesic effect mediated through peripheral receptors.[22]

Opioid analgesics differ in their potency, speed of

onset, duration of action, and route of administration. The most common side effects are sedation, respiratory depression, vomiting, enuresis, pruritus, and constipation. Although tolerance and dependence may each occur with opioid use, the risk of addiction with appropriate medical management is minimal.[6] Concerns about the development of dependence on the part of patients, physicians, and pharmacists lead to underuse or suboptimal dosing of opioids in pain management.[2]

Tramadol is a centrally acting weak μ-opioid receptor agonist that also possesses nonopioid mechanisms of action. Tramadol modulates monoaminergic pathways, increasing synaptic levels of norepinephrine and serotonin in central neurons.[23] The side effects of tramadol are less severe than those of other opioids and the risk of dependence is low.[2] There are no organ-damaging risks.

Nonopioid analgesics

Aspirin and acetaminophen are two of the most widely used analgesics and are effective for mild-to-moderate headache and pain of musculoskeletal origin. Acetaminophen apparently inhibits central prostaglandin synthesis and fever but has no anti-inflammatory effects. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are nonopioid analgesics that act peripherally at the site of tissue damage by blocking prostaglandin synthesis. Drugs in this class have varying degrees of anti-inflammatory, antipyretic, and analgesic properties as well as different side effects, time to onset of action, and duration of action. Aspirin, like other nonselective NSAIDs, inhibits both COX-1 and COX-2; therefore, gastrointestinal (GI) toxicity and bleeding are undesirable side effects of these analgesics. GI toxicity associated with NSAID use is substantial. Each year there are more than 100,000 NSAID-related hospitalizations, with mortality of rates of 5% to 10%.[24]

Ketorolac, a nonselective NSAID, is approved for the short-term management of moderately severe postoperative acute pain. Ketorolac has the distinction of being the only non-narcotic analgesic available in a parenteral formulation that can be administered for the relief of acute pain. Because ketorolac is nonselective, it may be contraindicated in patients with GI disorders, hypertension, renal disease, and in patients on anticoagulation therapy. Caution must be used when administering ketorolac to volume-depleted patients. All of the above conditions may complicate the perioperative state.[25]

Coxibs in acute and perioperative pain management

Postsurgical pain is frequently undertreated.

COX-2–selective inhibitors are effective opiate-sparing analgesic agents in the perioperative setting and are a sound addition to balanced analgesia.

Unlike opioids and nonselective NSAIDs, COX-2–selective inhibitors do not have serious side effects (eg, bleeding) that can negatively affect surgical outcomes.

Inhibition of COX-2–mediated prostaglandin synthesis reduces nociceptive pain and prevents inflammatory pain that leads to hyperalgesia.

Analgesics provide more effective pain relief when used preemptively, owing to the prevention of peripheral sensitization.

Rofecoxib has a clinically proven longer duration of action than celecoxib and nonselective NSAIDs, making it more appropriate for preemptive analgesia.

COX-2–selective inhibitors

COX-2–selective inhibitors have rapidly become an important resource for pain treatment. Rofecoxib and celecoxib are COX-2–selective inhibitors (coxibs) with anti-inflammatory, antipyretic, and analgesic properties similar to other NSAIDs and are indicated for the treatment of acute pain. Clinical data have shown that COX-2–selective inhibitors have efficacy equivalent to NSAIDs but have significantly lower risk of side effects such as GI ulceration, inhibition of platelet aggregation, or increased bleeding time.[26–28] Therefore, COX-2–selective inhibitors have potential for use in the perioperative setting.

Antidepressants and anticonvulsants

Tricyclic antidepressants may offer relief for chronic pain. Analgesic activity of tricyclic agents is initiated sooner and at a lower dose than their antidepressant activity. In addition to their effect on neurotransmitters (eg, serotonin and norepinephrine), antidepressants may potentiate opioid analgesia.[6] Tricyclic antidepressants have significant side effects. Unfortunately, newer serotonin-selective reuptake inhibitors, such as fluoxetine, lack efficacy in pain relief. Some atypical antidepressants that are more tolerable than tricyclics, such as venlafaxine and mirtazapine, are efficacious in the management of chronic pain. Anticonvulsants, such as carbamazepine, phenytoin, and the newer agent gabapentin, help relieve neuropathic pain.[6]

Topical agents

Bupivacaine and capsaicin are used topically to treat pain associated with neuralgia, neuropathy, and arthritis. Capsaicin is thought to inhibit the synthesis, transport, and release of substance P.[2] Lidocaine (5%) patches may relieve postherpetic neuralgia.[29]

Other analgesic agents

Ketamine inhibits the actions of excitatory amino acids, which are thought to be critical mediators of nociception and hyperalgesia. Clonidine, a central α-receptor agonist, modulates monoamine release and has been effectively used in multimodal regimens.

EVOLVING CONCEPTS IN PERIOPERATIVE ANALGESIA

Preemptive analgesia

The types of acute and chronic pain (discussed earlier), and analgesic strategies to resolve them, are diagrammed in **Figure 1**. An evolving concept in perioperative pain management is the use of preemptive analgesia (**Figure 1**).[9,30] The pain and inflammation that result from surgery normally cause increased prostaglandin production and sensitization. If analgesia is administered before painful stimuli and tissue damage, hypersensitivity can be circumvented and hyperalgesia and central sensitization prevented.[9,30] Accordingly, the use of long-acting analgesic agents before surgery can avert the establishment of a sensitized state in the peripheral nervous system, greatly diminishing the degree and persistence of postoperative pain.

Balanced analgesia

Balanced analgesia uses a combination of topical anesthetics, opioids, and NSAIDs to improve analgesic efficacy and safety.[31,32] In perioperative settings, this strategy should be used whenever possible as it has the advantage of decreasing the doses and thereby the adverse effects of each drug. While opioid-sparing, balanced analgesia provides enhanced pain relief compared with opioids or local anesthetics alone.[23]

COX-2–selective inhibitors have been shown to be efficacious in the prevention of hyperalgesia when used postoperatively as part of a balanced approach to analgesia. Their tolerability and the nonadditive nature of the dose-related adverse effects of opioids make the COX-2–selective inhibitors a particularly useful resource in combination with opioids.[6]

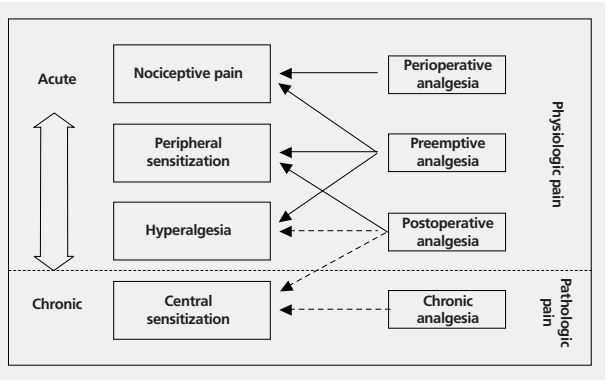

FIGURE 1. Analgesic strategies for pain management. The temporal progression of pain and approaches (and their argets) to the initiation and maintenance of analgesia. Arrows show effector pathways (dotted lines indicate lower efficacy). Adapted with permission from Kissin I. Preemptive analgesia. Anesthesiology 2000; 93:1138–1143.[30]

Though there are many analgesic choices for treating pain in general, there are fewer choices and more limitations when using analgesics in the perioperative setting. A multitude of factors come into play when a patient needs pain relief for a surgical procedure and concerns about hepatic, cardiac, and renal function are paramount. Also, patients often cannot take drugs orally and may benefit from preoperative longer-acting analgesic agents and analgesic adjuvants. Additionally, in the case of invasive surgery, platelet aggregation should not be compromised, unless risk of thrombosis signals a specific need for antithrombotic agents. Bleeding is a concern with the use of nonselective NSAIDs, and so, they are usually discontinued prior to surgery. Ketorolac presents particular concerns due to its renal effects: it may cause volume depletion and precipitate renal failure and is, therefore, contraindicated for preoperative analgesia. Despite the benefit of nonselective NSAIDs as part of a balanced analgesic regimen, their potential adverse effects may ultimately compromise pain relief. This obstacle to nonselective NSAID use may be effectively overcome with the use of COX-2–selective inhibitors.[33]

COX-2–SELECTIVE INHIBITORS IN PREEMPTIVE ANALGESIA

In the perioperative setting, preemptive analgesia can be achieved with NSAIDs, COX-2–selective inhibitors, acetaminophen, and longer-acting

TABLE 2
SUMMARY OF ACUTE PAIN STUDIES OF COX-2–SELECTIVE INHIBITORS

Model	N	Design	Drugs	Results
Primary dysmenorrhea[34]	127	R, DB PC, AC, crossover	Rofecoxib 25 or 50 mg initially plus rofecoxib 25 mg as needed Naproxen 550 mg BID	Rofecoxib 25 and 50 mg superior to placebo* Rofecoxib onset, peak, and overall analgesia comparable to naproxen Rofecoxib duration longer than naproxen*
Postoperative dental pain[35]	151	R, DB, PC, AC	Rofecoxib 50 mg Ibuprofen 400 mg	Rofecoxib superior to placebo† Rofecoxib onset, peak and overall analgesia not different from ibuprofen Rofecoxib duration longer than ibuprofen†
Postoperative dental pain[36]	272	R, DB, PC, AC	Rofecoxib 50 mg Celecoxib 200 mg Ibuprofen 400 mg	Rofecoxib and celecoxib superior to placebo‡ Rofecoxib superior to celecoxib for onset, peak, and overall duration of analgesia§ Rofecoxib and celecoxib similar to ibuprofen
Postoperative dental pain[37]	393	R, DB, PC, AC	Rofecoxib 50 mg Codeine 60 mg plus acetaminophen 600 mg	Rofecoxib superior to codeine/acetaminophen for peak, overall, and duration of analgesia‡ Rofecoxib comparable to codeine/acetaminophen for onset Codeine/acetaminophen group had significantly more adverse effects than rofecoxib group‡
Postoperative dental pain[38]	304	R, DB, PC AC	Parecoxib 20 mg IM or IV Parecoxib 40 mg IM or IV Ketorolac 60 mg IV	Parecoxib (all doses and routes) superior to placebo¶ Parecoxib routes and dosages comparable to ketorolac except parecoxib 40 mg had longer duration†

R = randomized; DB = double blind; PC = placebo controlled; PG = parallel group; AC = active comparator; IM = intramuscular; IV = intravenous; BID = twice daily.
*$P \leq .006$.
†$P < .05$.
‡$P < .001$.
§$P < .001$; $P < .003$; $P < .001$, respectively.
¶$P \leq .05$.

opioids such as codeine and propoxyphene. COX-2–selective inhibitors, or coxibs, offer advantages over nonselective NSAIDs due to their lack of COX-1 inhibition. They do not affect platelet function nor do they increase the risk of bleeding, and they are associated with less GI toxicity than nonselective NSAIDs. COX-2–selective inhibitors lack the serious side effects of opioids and complement other analgesic agents. These factors, combined with their duration of action, have prompted studies of their use in preemptive analgesia.

Acute pain

Adequate relief of acute pain may be dependent on several factors such as time to onset of analgesia, maximum analgesic effect, and duration of analgesic effect. Several key studies of coxibs in acute pain are summarized in **Table 2**. Relevant conclusions are briefly detailed here.

Primary dysmenorrhea is caused by prostaglandin-induced uterine hyperactivity and is usually treated with nonselective NSAIDs. The pain associated with dysmenorrhea is similar to perioperative pain, particularly that of abdominal surgery, and lasts about 72 hours. As it is associated with both acute and recurring pain, dysmenorrhea requires analgesic relief on a cyclical basis. Concerns about GI toxicity from the effects of long-term nonselective NSAID use are justified.

Rofecoxib is indicated for the treatment of dysmenorrhea and, at doses of 25 mg or 50 mg, provided analgesic relief comparable to naproxen (550 mg BID) in 127 women with a history of primary dysmenorrhea.[34] The main endpoints used in the study were total pain, difference in pain intensity over an 8-hour period, patient global evaluation, and time to remedication.

Patients frequently receive nonselective NSAIDs

for acute pain associated with dental surgery. A study of rofecoxib 50 mg (n = 50) and ibuprofen 400 mg (n = 51) for pain after oral surgery, compared with placebo (n = 50), assessed efficacy by evaluating pain intensity and pain relief at 12 intervals during a 24-hour period.[35] Additional primary assessments included the TOPAR8, which represents the time-weighted pain-relief score up to 8 hours.[35] Rofecoxib and ibuprofen both resulted in significantly better TOPAR8 scores than placebo ($P < .05$), but patients randomized to rofecoxib had longer lasting pain relief compared with the ibuprofen group ($P = .039$). Fewer patients (28%) receiving rofecoxib took rescue medication within the 24-hour period compared with those receiving ibuprofen (82.4%). Notably, tolerability was greatest for rofecoxib.[35]

Another study of pain due to molar excision evaluated rofecoxib (50 mg) and celecoxib (200 mg), each compared with ibuprofen, through the 24-hour period following surgery.[36] Rofecoxib had analgesic effects on all measures that were superior to celecoxib, including overall analgesic effect (TOPAR8), time to onset of pain relief, peak pain relief, and duration of effect. Notably, and as shown in other studies, rofecoxib had analgesic efficacy comparable to ibuprofen but with longer duration ($P < .05$) (**Figure 2**).[36]

A similar double-blind, randomized study of postoperative dental pain compared the efficacy of rofecoxib 50 mg with codeine 60 mg plus acetaminophen 600 mg in 393 patients.[37] The overall analgesic effect of rofecoxib was greater than that of codeine/acetaminophen for TOPAR8 ($P < .001$), as was the patient global assessment of response to therapy (PGART) at 6 hours ($P < .001$). The onset of analgesic effect was similar for rofecoxib and codeine/acetaminophen, but the peak analgesic effect was significantly greater in the rofecoxib group ($P < .001$). As seen in other studies, duration of analgesic effect was greater with rofecoxib. More patients in the codeine/acetaminophen group experienced adverse events overall ($P < .05$) and nausea in particular ($P < .001$) compared with rofecoxib.[37]

In a study of intramuscularly or intravenously administered NSAID for postoperative dental pain, the experimental parenteral coxib, parecoxib, was compared with the nonselective NSAID ketorolac.[38] Although generally comparable on all experimental measures (time-specific pain intensity, pain relief, time to onset of analgesia, and time to use of rescue medication), parecoxib effected a longer duration of analgesia than did ketorolac ($P \leq .05$).[38]

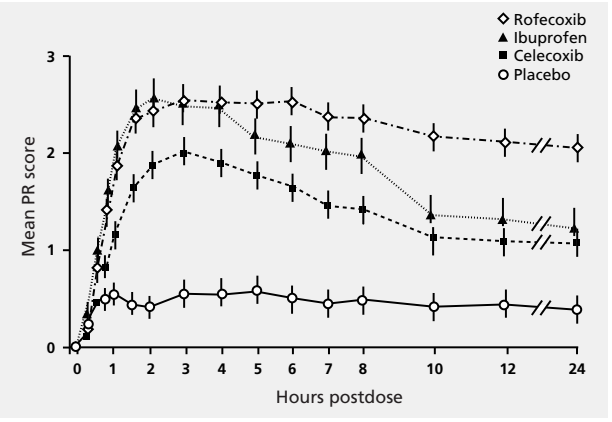

Figure 2. Mean (± SE) pain relief (PR) in patients experiencing moderate to severe postoperative dental pain over the 24 hours after dosing with rofecoxib 50 mg, ibuprofen 400 mg, celecoxib 200 mg, or placebo. Patients who used rescue medication are included (last observation carried forward). Reprinted with permission of the publisher. From Malmstrom K et al. Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: a randomized, placebo- and active-comparator-controlled clinical trial. Clin Ther 1999; 21:1653–1663. Copyright 1999 by Exerpta Medica Inc.[36]

Studies show that, for commonly employed regimens, rofecoxib is superior to placebo and comparable to commonly used nonselective NSAIDs, and codeine plus acetaminophen, by many of the criteria for determining overall analgesic efficacy. Similar results may hold for parecoxib compared with ketorolac. Time to onset, peak effect, and duration of analgesia are important factors.

Celecoxib has been recently approved for acute pain: 400 mg followed by 200 mg every 12 hours as needed.[39] Another oral coxib, valdecoxib, was recently approved for osteoarthritis, rheumatoid arthritis, and menstrual pain.[40]

Preemptive and postsurgical analgesia

As discussed earlier, the use of long-lasting analgesics *before* surgery may help to avoid the establishment of a sensitized state and result in diminished postoperative pain. **Table 3** summarizes data on coxibs in preemptive and postsurgical analgesia. Some relevant details are presented here.

In the ambulatory setting, preoperative rofecoxib (50 mg, n = 19), acetaminophen (2,000 mg, n = 16), or a combination of rofecoxib 50 mg plus acetaminophen 2,000 mg (n = 14), compared with a con-

TABLE 3
SUMMARY OF COX-2–SELECTIVE INHIBITORS USED IN PREEMPTIVE AND POSTSURGICAL STUDIES

Model	N	Design	Drugs	Results
PREEMPTIVE ANALGESIA				
Ear, nose, and throat surgery[41]	68	R, DB PC, AC	Vitamin C (control) Acetaminophen 2,000 mg Rofecoxib 50 mg Rofecoxib 50 mg plus acetaminophen 2,000 mg	Rofecoxib superior to control* Rofecoxib superior to acetaminophen* Rofecoxib decreased postsurgical opioid use* Rofecoxib alone or with acetaminophen comparable
Knee arthroplasty[42]	21	R, DB PC	Rofecoxib 25 mg 3 days prior to surgery	Rofecoxib superior to placebo†
Spinal fusion[43]	60	R, DB, PC	Rofecoxib 50 mg Celecoxib 200 mg	Rofecoxib and celecoxib superior to placebo‡ Rofecoxib and celecoxib groups used less postsurgical opioids§ Rofecoxib superior to celecoxib for duration of analgesia*
Lower abdominal surgery[44]	25	R, DB PC	Rofecoxib 25 or 50 mg	Rofecoxib 50 mg superior to placebo* Rofecoxib group used less postsurgical opioids than placebo*
POSTSURGICAL ANALGESIA				
Orthopedic surgery[45]	218	R, DB PC, AC	Rofecoxib 50 mg (day 1), then 25 or 50 mg/day (days 2–5) Naproxen 550 mg	Rofecoxib 50 mg superior to placebo* Rofecoxib similar to naproxen Rofecoxib decreased postsurgical opioid use¶
Orthopedic surgery[46]	418	R, DB PC, AC	Celecoxib 200 mg TID Hydrocodone 10 mg plus acetaminophen 1,000 mg	Single-dose assessment (8 hours): Hydrocodone/acetaminophen superior to placebo at 1.5 hours Celecoxib superior to placebo at 8 hours‡ Multiple-dose assessment (5 days): Celecoxib 200 mg TID superior to hydrocodone/acetaminophen*

R = randomized; DB = double blind; PC = placebo controlled; PG = parallel group; AC = active comparator; TID = three times daily.
*$P < .05$.
†$P < .001$.
‡$P < .0001$.
§$P < .0001$ and $P < .03$, respectively.
¶$P = .005$.

trol group given vitamin C (500 mg, n = 19), were evaluated in patients undergoing ear, nose, and throat surgery.[41] Patients took medication 30 minutes before surgery and the morning after surgery. For overall analgesic efficacy, preoperative rofecoxib was significantly more effective than either placebo or acetaminophen ($P < .05$); rofecoxib also decreased the need for rescue opioid (fentanyl). Notably, the addition of acetaminophen to rofecoxib did not significantly improve analgesic efficacy.[41]

In patients undergoing total knee arthroplasty, the safety and efficacy of the preoperative and postoperative administration of rofecoxib was evaluated.[42] All patients were required to discontinue NSAID use 10 days prior to surgery and for 7 days received no medication. Three days before surgery patients were randomized to either placebo (n = 11) or rofecoxib 25 mg (n = 10). Pain measurements at rest and while moving were made during the 7-day drug-free period and the 3 days leading up to surgery, and other hematologic variables were measured, including intraoperative blood loss and postoperative measures of hemoglobin, hematocrit, platelet count, prothrombin time, and international normalized ratio. Rofecoxib resulted in significantly improved pain scores on all measurements. There were no differences in intraoperative bleeding or the variables used to assess hemodynamic factors.[42]

Reuben and Connelly also investigated the preemptive use of rofecoxib 50 mg (n = 20) and celecoxib 200 mg (n = 20) compared with placebo (n = 20) in patients undergoing spinal fusion surgery.[43] At the end of the study, patients in the placebo group had significantly higher cumulative dosages of morphine than did patients in either the celecoxib group ($P < .03$) or the rofecoxib group ($P < .0001$) (**Figure 3**).[43] The morphine dosage was significantly lower for patients in the rofecoxib group at each measurement interval compared with placebo; patients in the celecoxib group consumed as much or more morphine in the last four of the six intervals as did patients in the placebo group. No significant increase in intraoperative bleeding in patients receiving either coxib was observed.[43]

Preliminary results from a study evaluating the effect of preoperative rofecoxib (25 mg and 50 mg) on postsurgical patient-controlled analgesia (PCA) morphine usage and measurements of effort-dependent pain found that patients randomized to rofecoxib 50 mg had significantly better visual analog scale (VAS) pain scores and consumed significantly less morphine than their counterparts in the other two study groups following elective abdominal surgery.[44] The rofecoxib 50 mg group also had superior pulmonary function relative to the other two groups.

Studies of coxibs for preemptive analgesia show that a single dose of rofecoxib or celecoxib before surgery diminished both postoperative pain and postsurgical morphine use. Rofecoxib was more effective than celecoxib for preemptive analgesia. Both drugs were similarly analgesic over the initial postoperative period, but one preoperative dose of rofecoxib provided enduring relief.

For postsurgical pain, rofecoxib 50 mg (given as 50 mg on day 1, then 25 or 50 mg on days 2 to 5) was superior to placebo ($P < .05$) and similar to naproxen for all single-dose measures of pain relief following orthopedic surgery (**Table 3**).[45] Furthermore, the rofecoxib 50-mg group used less narcotic analgesia ($P = .005$) and reported less pain on global evaluations ($P = .041$) than did the placebo group.

In another study of postorthopedic surgical pain, celecoxib (200 mg 3 times daily) compared with hydrocodone 10 mg plus acetaminophen 1,000 mg resulted in significantly lower maximum pain intensity, fewer doses of medication, and superior scores on the American Pain Society Patient Questionnaire (all $P \leq .013$).[46] Fewer patients taking celecoxib experienced adverse events compared with those taking hydrocodone plus acetaminophen (43% vs 89%; $P < .001$).[46]

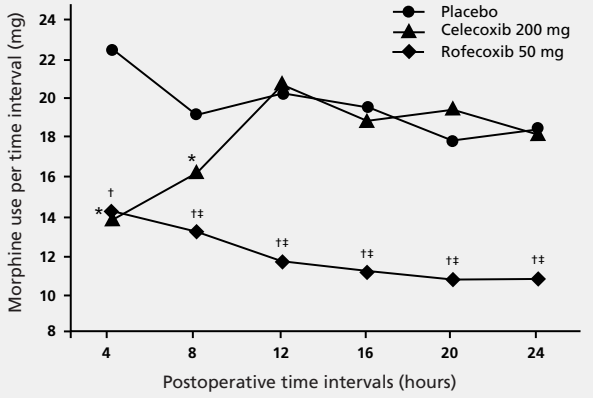

Figure 3. PCA morphine consumption at each postoperative time interval in patients undergoing spinal fusion surgery who received preemptive analgesia with a COX-2–selective inhibitor or placebo. Reprinted with permission from Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000; 91:1221–1225.[43]

Other known side effects of nonselective NSAIDs include inhibition of osteogenic activity in patients undergoing spinal fusion. Preclinical data showed that rofecoxib does not inhibit osteogenic activity. Currently, there is an ongoing double-blind controlled clinical trial to verify that rofecoxib does not interfere with spinal fusion. Additionally, a retrospective trial involving more than 300 patients who underwent spinal fusion surgery showed that rofecoxib was associated with a nonunion rate similar to that of placebo from a historical trial.[47]

■ DISCUSSION

The importance of managing patients' pain reflects the core value medicine places on the alleviation of suffering. Achieving this goal is a complex mission, and strategies must consider the biologic and psychosocial aspects of pain.

Strategies to relieve surgical pain have traditionally been dominated by postoperative opioid analgesia. The demand for opioid-sparing analgesic options, however, has been underscored by the desire for better pain management in general and concern

about opioid side effects in particular. Reliance on opioids often leads healthcare providers to balance effective pain management with prodigious efforts to avoid complications from side effects.

Developments in the pharmacology of pain have created expanding vistas, allowing discovery of interventions that are both safer and more efficacious while being appropriate to contemporary understanding of clinical pain management. Understanding of pain mechanisms has revealed the importance of proactive interventions in analgesia that aim to prevent initiation of hyperalgesia and central sensitization through preemptive analgesia. An appreciation of balanced approaches to analgesia has allowed for safer pharmacologic strategies for analgesia.

Nonselective NSAIDs are not used in the perioperative setting. The analgesic benefit of NSAIDs, however, provides a germane standard of analgesic efficacy. Coxibs, the COX-2 selective inhibitors, have emerged as a class of analgesic agents that offers pain relief similar to nonselective NSAIDs without compromising platelet aggregation or causing GI toxicity.

Clinical data evaluating the use of coxibs before or after various surgical procedures showed that there was no increased blood loss associated with rofecoxib or celecoxib use. Moreover, many surgical outcomes (eg, time to recovery) often depend on how soon a patient can regain mobility. Across studies, patients with lower opioid usage regained mobility faster than their more opioid-dependent counterparts. This feature has obvious value in both the hospital and outpatient settings.

Studies of pain are limited by the subjectivity of pain and the lack of a gold standard for pain measurement. Most studies rely on the VAS as an important endpoint for measuring pain in the perioperative setting. Nevertheless, analgesic efficacy is the outcome of many factors: time to onset of action, duration of action, side effects, maximum pain relief, usage of rescue medication, and any other specific factors relevant in a particular acute pain model. Multiple studies of pain using these criteria have shown that coxibs are an effective analgesic option in the treatment of acute and perioperative pain. Additionally, clinical data have shown that rofecoxib has a longer duration of action than celecoxib or ibuprofen when used in both the preoperative and postoperative settings. The confluence of clinical data from randomized, blinded studies suggests that COX-2–selective inhibitors contribute to an enhanced standard of care for patients.

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