The Changing Role of Non-Opioid Analgesic Techniques in the Management of Postoperative Pain

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Given the expanding role of ambulatory surgery and the need to facilitate an earlier hospital discharge, improving postoperative pain control has become an increasingly important issue for all anesthesiologists. As a result of the shift from inpatient to outpatient surgery, the use of IV patient-controlled analgesia and continuous epidural infusions has steadily declined. To manage the pain associated with increasingly complex surgical procedures on an ambulatory or short-stay basis, anesthesiologists and surgeons should prescribe multimodal analgesic regimens that use non-opioid analgesics (e.g., local anesthetics, nonsteroidal antiinflammatory drugs, cyclooxygenase inhibitors, acetaminophen, ketamine, α 2-agonists) to supplement opioid analgesics. The opioid-sparing effects of these compounds may lead to reduced nausea, vomiting, constipation, urinary retention, respiratory depression and sedation. Therefore, use of non-opioid analgesic techniques can lead to an improved quality of recovery for surgical patients.

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The current armamentarium of analgesic drugs and techniques for the management of postoperative pain continues to grow at a rapid rate. However, effective treatment of acute postsurgical pain still poses unique challenges for practitioners (1). An increasing number of complex operations are being performed on an outpatient basis for which the use of conventional opioid-based IV patient-controlled analgesia (PCA) and central neuraxial (spinal and epidural) analgesia are not practical techniques for pain management. This expanding patient population requires a perioperative analgesic regimen that is highly effective, has minimal side effects, is intrinsically safe, and can be easily managed away from the hospital or surgical center (2).

Adequacy of postoperative pain control is one of the most important factors in determining when a patient can be safely discharged from a surgical facility and has a major influence on the patient's ability to resume their normal activities of daily living (3). Perioperative analgesia has traditionally been provided by opioid analgesics. However, extensive use of opioids is associated with a variety of perioperative side effects, such as ventilatory depression, drowsiness and sedation, postoperative nausea and vomiting (PONV), pruritus, urinary retention, ileus, and constipation, that can delay hospital discharge (4). Intraoperative use of large bolus doses or continuous infusions of potent opioid analgesics may actually increase postoperative pain as a result of their rapid elimination and/or the development of acute tolerance (5). In addition, it has been suggested by the Joint Commission on Accreditation of Healthcare Organizations that excessive use of postoperative opioid analgesics leads to decreased patient satisfaction. Partial opioid agonists (e.g., tramadol) are also associated with increased side effects (e.g., nausea, vomiting, ileus) and patient dissatisfaction compared with both opioid (6) and non-opioid (7,8) analgesics.

Therefore, anesthesiologists and surgeons are increasingly turning to non-opioid analgesic techniques as adjuvants for managing pain during the perioperative period to minimize the adverse effects of analgesic medications. Multimodal or "balanced" analgesic techniques involving the use of smaller doses of opioids in combination with non-opioid analgesic

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Table 1. Non-opioid Drugs and Nonpharmacologic Techniques Used for Minimizing Pain After Surgery

- Local anesthetics
  - lidocaine, 0.5%–2% SQ/IV
  - bupivacaine, 0.125%–0.5% SQ
  - levobupivacaine, 0.125%–0.5% SQ
  - ropivacaine, 0.25%–0.75% SQ
- Nonsteroidal antiinflammatory drugs
  - ketorolac, 15–30 mg PO/IM/IV
  - diclofenac, 50–100 mg PO/IM/IV
  - ibuprofen, 300–800 mg PO
  - indomethacin, 25–50 mg PO/PR/IM
  - naproxen, 250–500 mg PO
  - celecoxib, 200–400 mg PO
  - rofecoxib, 25–50 mg PO
  - valdecoxib, 20–40 mg PO
  - parecoxib 20–40 mg IV
- Miscellaneous analgesic compounds
  - acetaminophen, 0.5–2 g PO/PR/IV
  - propacetamol, 0.5–2 g IV
  - ketamine, 10–20 mg PO/IM/IV
  - dextromethorphan, 40–120 mg PO/IM/IV
  - amantadine, 200–400 mg PO/IV
  - clonidine, 0.15–0.3 mg PO/TC/IM/IV
  - dexmedetomidine, 0.5–1 μg/kg, followed by 0.4–0.8 μg/kg/h IV
  - gabapentin, 600–1200 mg PO
  - magnesium, 30–50 mg/kg, followed by 7–15 mg/kg/h IV
  - neostigmine, 1–10 μg/kg EPI/IT
- Nonpharmacologic therapies
  - transcutaneous electrical nerve stimulation (TENS)
  - transcutaneous acupoint electrical stimulation (TAES)
  - acupuncture-like transcutaneous electrical nerve stimulation (ALTENS)

PO = oral; PR = per rectum; SQ = subcutaneous/tissue; IM = intramuscular; IV = intravenous; TC = transcutaneous; EPI = epidural; IT = intrathecal.

Adapted from White (4).

Table 2. Techniques for Administering Local Anesthesia During the Perioperative Period

- Peripheral nerve blocks
  - ilioinguinal/hypogastric (e.g., herniorrhaphy)
  - paracervical (e.g., dilation/curettage, cone biopsy)
  - dorsal penile (e.g., circumcision)
  - peroneal/femoral/saphenous/tibial/sural (e.g., podiatric)
  - femoral/obturator/lateral femoral cutaneous/sciatic (e.g., leg)
  - brachial plexus/axillary/ulnar/median/radial (e.g., arm/hand)
  - peribulbar/retrobulbar (e.g., ophthalmologic procedures)
  - mandibular/maxillary (e.g., oral surgery)
  - intravenous regional (Bier block) (e.g., arms, legs)
  - intercostal/paravertebral (e.g., breast surgery)
- Tissue infiltration and wound instillation
  - cosmetic procedures (e.g., blepharoplasty, nasal, septum, endosinus)
  - excision of masses and biopsies (e.g., breast, axilla, lipomas)
  - field blocks or instillation technique (e.g., hernia repair, vasovasotomy)
  - laparoscopic procedures (e.g., cholecystectomy, tubal ligation)
  - arthroscopic procedures (e.g., knee, shoulder, wrist, ankle)
- Topical analgesia
  - eutectic mixture of local anesthetics (EMLA®) (e.g., skin lesions)
  - lidocaine spray (e.g., bronchoscopy, endoscopy, hernia repair)
  - lidocaine gel or cream (e.g., circumcision, urologic, oral surgery)
  - cocaine paste (e.g., nasal, endosinus surgery)

Adapted from White (4).

drugs, such as local anesthetics, ketamine, acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), are becoming increasingly popular approaches to preventing pain after surgery (Table 1) (9–11). This review will discuss recent evidence supporting the use of non-opioid analgesic drugs and techniques during the perioperative period for facilitating the recovery process.

Local Anesthetic Techniques

The routine use of peripheral nerve blocks and wound infiltration with long-acting local anesthetics as an adjuvant to local, regional, and general anesthetic techniques can improve postoperative pain management after a wide variety of surgical procedures (Table 2) (4). When administered before surgery, these simple techniques can also decrease anesthetic and analgesic requirements during surgery, as well as reduce the need for opioid-containing analgesics postoperatively. More effective pain relief in the early postoperative period, as a result of the residual sensory block produced by local anesthetics, facilitates recovery by enabling earlier ambulation and discharge home (i.e., "fast-track" recovery) (12–14). In addition, use of local anesthetic-based techniques for preventing pain can decrease the incidence of PONV because of their opioid-sparing effects. However, these techniques are most effective for superficial procedures and the duration of analgesia lasts for only 6–8 h.

Blockade of the ilioinguinal and iliohypogastric nerves significantly decreases opioid analgesic requirements in both children and adults undergoing inguinal herniorrhaphy by providing 6–8 h of postoperative pain relief (15,16). Similarly, a subcutaneous ring block of the penis provides effective perioperative analgesia for circumcision (17). Local anesthetic infiltration of the mesosalpinx significantly decreases pain and cramping after laparoscopic tubal ligation (18).

Simple instillation of local anesthetic after removal of the gallbladder also reduced right upper quadrant and shoulder pain (10,19). Pain after arthroscopic shoulder surgery was decreased significantly by a suprascapular nerve block (20) and pain after knee surgery was minimized with a femoral nerve block (21). However, more complete perioperative analgesia for painful shoulder and knee procedures requires use of interscalene brachial plexus (22) and combined femoral, obturator, lateral femoral cutaneous, and sciatic nerve (23) blocks, respectively. Although additional preparation time may be required when major peripheral nerve blocks are performed before surgery, these techniques can offer significant advantages compared with general and spinal anesthesia with respect to pain control in the postoperative period (12,13,22,23).

It has been suggested that performing neural blockade with local anesthetics before surgical incision prevents the nociceptive input from altering excitability of the central nervous system by preemptively blocking the *N*-methyl-D-aspartate- (NMDA) induced "wind up" phenomena and subsequent release of inflammatory mediators (24). The concept of preemptive analgesia, or treating postoperative pain by preventing establishment of central sensitization, seems intuitively logical. However, the clinical relevance of preemptive analgesia has been questioned. Only a small number of well controlled clinical studies have demonstrated any benefit of preincisional versus postincisional analgesic administration (25,26). A quantitative systematic review by Møiniche et al. (27) stated that evidence is still lacking to support the claim that the timing of single-dose or continuous postoperative pain treatment is critically important in the management of postsurgical pain. These investigators concluded that there was no convincing evidence that preemptive treatment with centrally or peripherally administered local anesthetics, NSAIDs, opioid analgesics, or ketamine offers any advantage with respect to postoperative pain relief when compared with a similar analgesic regimen administered after the surgical incision (27). Nevertheless, preincisional local anesthetic administration offers an obvious advantage over infiltration at the end of surgery because it can provide supplemental intraoperative analgesia as well as effective analgesia in the early postoperative period after emergence from anesthesia.

Preincisional infiltration of the surgical wound site with local anesthetics, combined with general anesthesia, is clearly superior to general or spinal anesthesia alone in reducing postoperative pain (28,29). For example, preincisional infiltration of the tonsillar bed with bupivacaine decreased the intensity of both constant pain and pain on swallowing fluids for up to 5 days after tonsillectomy procedures (29). Paracervical block with 0.5% bupivacaine also reduced pain and the need for opioid analgesics after vaginal hysterectomy under general anesthesia (30). Preincisional ilioinguinal-iliohypogastric nerve block not only improves perioperative pain control for inguinal hernia repair but also reduces the need for oral opioid-containing analgesics in the postdischarge period (16). Although local infiltration can reduce incisional pain after laparoscopic cholecystectomy (31–34), some investigators have actually reported that infiltration of the trocar sites at the end of surgery provided better pain relief than when the local anesthetic was given before incision (32). The overall analgesic efficacy of trocar wound infiltration after laparoscopic surgery remains controversial (35).

Although preincisional infiltration of the operative site with local anesthetics remains popular for reducing the perioperative opioid analgesic requirement, other simpler local anesthetic delivery systems (e.g., topical applications) have been described (36–40). Topical analgesia with a lidocaine aerosol was effective in decreasing pain, as well as the opioid analgesic requirement, after inguinal herniorrhaphy in adults (36), and instillation of 0.25% bupivacaine before surgical closure compared favorably to an ilioinguinal-iliohypogastric nerve block in children undergoing hernia repair (37). Furthermore, the simple application of topical lidocaine jelly or ointment, as well as eutectic mixture of local anesthesia (EMLA) cream, have been shown to be as effective as peripheral nerve blocks or parenteral opioids in providing pain relief after outpatient circumcision (38–40). Use of a 5% lidocaine patch has also been reported to be effective in providing peripheral analgesia (41). However, further studies are needed to define the role (if any) of this analgesic device in the postoperative period.

Intracavitary instillation of local anesthetics is another simple, yet effective, technique for providing pain relief during the early postoperative period after laparoscopic and arthroscopic procedures. For example, when 80 mL of lidocaine 0.5% or bupivacaine 0.125% was administered intraperitoneally at the start of the laparoscopic procedure, postoperative scapular pain and the need for opioid analgesic during the first 48 h after surgery were significantly reduced (42). Compared with a control group receiving saline, use of intraperitoneal bupivacaine 0.5% (15–30 mL) also led to a larger percentage of patients going home on the day of surgery (79% versus 43%) (43). However, other studies involving intraperitoneal administration of local anesthetics during laparoscopy report inconsistent effects on postoperative pain and the need for opioid analgesics (44–54). Some investigators have suggested that the beneficial effects of intraperitoneal bupivacaine are transient and have little impact on patient recovery (49). Furthermore, when bupivacaine was injected at the preperitoneal fascial plane during extraperitoneal laparoscopic hernia repair, it also

failed to reduce postoperative pain (55). Subfacial infiltration with bupivacaine 0.5% at the trochar and incision sites reduced pain and the length of stay after laparoscopic nephrectomy procedures (56). Yndgaard et al. (57) demonstrated that subfascially administered lidocaine was significantly more effective than subcutaneous injection in reducing pain after inguinal herniotomy. It is obvious that the location, volume, and timing of the local anesthetic administration are key factors in determining efficacy of intraperitoneal instillation in preventing pain after both superficial and laparoscopic surgery (19,43,53).

Analogous to intraperitoneal administration, intrapleural instillation of local anesthetic solutions has been reported to improve pain control after laparoscopic surgery (58–66). Some investigators report that interpleural bupivacaine produced more effective analgesia than intraperitoneal bupivacaine (66) and compared favorably with epidural bupivacaine (58) after laparoscopic cholecystectomy. Compared with standard opioid analgesics, intrapleural bupivacaine achieved better pain relief and greater improvement in postoperative pulmonary function (59,64). In contrast, Oxorn and Whatley (65) reported that postoperative pulmonary mechanics were worsened after intrapleural bupivacaine. Adverse effects on pulmonary function (resulting from muscle weakness) and the risk of systemic local anesthetic toxicity (resulting from rapid systemic absorption) are the major concerns with this technique (66,67). Although intercostal nerve blocks can also improve pain relief after cholecystectomy procedures, this does not necessarily lead to improved pulmonary function (68).

Local anesthetics are also commonly injected into joint spaces to provide analgesia during and after arthroscopic procedures (69,70). In a placebo-controlled study, intraarticular instillation of 30 mL of 0.5% bupivacaine reduced opioid requirements and facilitated early mobilization and discharge after knee arthroscopy (70). In a follow-up study, a combination of intraarticular bupivacaine and systemic ketorolac (60 mg) further decreased pain in the early postoperative recovery period (71). In addition to the local anesthetics, a wide variety of other adjuvants (e.g., morphine, ketorolac, triamcinolone, and clonidine) have also been injected into the intraarticular space to decrease postarthroscopic pain (72–77). Small-dose intraarticular morphine, 0.5–1 mg, combined with bupivacaine, appears to provide the longest-lasting and most cost-effective analgesia after knee arthroscopy (76,77). Although administering intraarticular morphine before knee surgery was reported to provide a longer duration of analgesia and greater opioid-sparing effects than when it was given at the end of surgery (77), the clinical advantage of preemptive intraarticular local anesthetic administration remains controversial (27).

Although local anesthetic supplementation decreases the severity of incisional pain in the early postoperative period, many patients still experience significant pain when the local anesthetic effect wears off. Therefore, continuous (78,79) and/or intermittent perfusion (80,81) of the surgical wound (or peripheral nerve) with local anesthetic solutions has been reintroduced as a way of extending local anesthetic-induced incisional pain relief into the postoperative period. In a study by White et al. (82), infusion of 0.5% bupivacaine (4 mL/h) at the median sternotomy site reduced postoperative pain and opioid analgesic requirement after cardiac surgery. As a result of the opioid-sparing effect, these patients recovered bowel and bladder function more rapidly. Similarly, wound instillation with 0.2% ropivacaine (5 mL/h) improved pain control after spine fusion surgery (83). These continuous local anesthetic infusion techniques can be modified to allow for patient-controlled local anesthetic administration after surgery (84,85).

Investigators have failed to find consistent improvement in pain scores or opioid-sparing effects when the local anesthetic was infused at the incision site after abdominal surgery (57,86–88). Efficacy of local anesthetic infusion systems is enhanced when the catheter is placed at the subfacial level or near a peripheral nerve. For example, a continuous popliteal-sciatic nerve block provides improved postoperative analgesia, decreased opioid use, and enhanced patient satisfaction after painful foot and ankle surgery (89,90). Similarly, a continuous infraclavicular brachial plexus block provides highly effective pain control after discharge in patients undergoing shoulder surgery (91). Although continuous local anesthetic infusions with concomitant PCA capability appears to be superior to a continuous infusion alone for prolonging nerve blocks (92,93), many patients elect not to use the PCA function on their electronic pumps (91).

When using a continuous local anesthetic infusion, analgesic efficacy is influenced by a wide variety of factors in addition to location of the catheter system, including the concentration and volume of the local anesthetic solution (82), as well as the accuracy and consistency of the pumps (94). The use of a disposable, nonelectronic infusion system may offer advantages over the electronic pump because its simplicity minimizes the need for troubleshooting (95). However, accuracy of the infusion rate of the nonelectronic pumps can change over time (94). Temperature changes also influence the infusion rate of elastomeric pumps, and battery life is a limiting factor for the electronic pumps (94). With these catheter delivery systems, the risk of infection appears to be small. However, bacterial colonization of the catheter is a common occurrence (96). Patient satisfaction and comfort when using these delivery systems outside the hospital is high, and more than 90% of the patients are

comfortable removing the catheter at home (97). Finally, combining local anesthetic infusion techniques with other analgesic modalities as part of multimodal analgesic therapy further improves pain control throughout the perioperative period (98).

Peripheral nerve block techniques are simple, safe, and highly effective approaches to providing perioperative analgesia. Use of long-acting local anesthetics for neural blockade techniques involving the upper (e.g., interscalene brachial plexus block) and lower (e.g., femoral-sciatic nerve block) extremities can facilitate an earlier discharge after major shoulder and knee reconstructive procedures, respectively (99,100). Availability of long-acting local anesthetics that claim less toxicity and greater selectivity with respect to sensory and motor blockade (e.g., ropivacaine) may further enhance the benefits of local anesthetic supplementation after both major and minor surgery.

Although ropivacaine 0.2% provides better pain relief with less motor impairment than lidocaine 1% for continuous interscalene brachial plexus block (101), its clinical advantages relative to equipotent concentrations of bupivacaine are less well established. Addition of adjuvants (e.g., epinephrine, clonidine) that can prolong postoperative analgesia and facilitate recovery when using central and peripheral nerve blocks may be of greater clinical importance (102,103). Interestingly, a more recent study (104) found that clonidine's use as an adjunct to ropivacaine as part of a continuous perineural infusion technique failed to reduce postoperative pain and oral analgesic usage or improve the patient's quality of sleep after upper extremity surgery when compared with the local anesthetic alone. Although pain control can be improved after orthopedic procedures by continuously infusing local anesthetic solutions (89,90,105–107), availability of longer-acting local anesthetic suspensions and "delayed release" formulations containing liposomes or polymer microspheres may minimize the need for continuous infusion catheter delivery systems in the future.

NSAIDs

Oral NSAIDs have long been used for treating nonsurgical pain syndromes because of their well known antiinflammatory, antipyretic, and analgesic properties. When parenteral preparations of NSAIDs (e.g., ketorolac, ketoprofen, diclofenac) became available, these drugs were more widely used in the management of acute perioperative pain. NSAIDs block the synthesis of prostaglandins by inhibiting cyclooxygenase (COX) types I and II, thereby reducing production of mediators of the acute inflammatory response. By decreasing the inflammatory response to surgical trauma, NSAIDs have been alleged to reduce peripheral nociception. Studies also suggest that the central response to painful stimuli is modulated by NSAID-induced inhibition of prostaglandin synthesis in the spinal cord (27).

Early reports suggested that parenteral NSAIDs possessed analgesic properties comparable to the traditional opioid analgesics (108–110) without opioid-related side effects (111,112). Compared with the partial opioid agonist tramadol, diclofenac produced better postoperative pain relief with fewer side effects after cardiac surgery (8). When administered as an adjuvant during outpatient anesthesia, ketorolac was associated with improved postoperative analgesia and patient comfort compared with fentanyl and the partial opioid agonist, dezocine (112,113). Other investigators reported that ketorolac provided postoperative pain relief similar to that of fentanyl but was associated with less nausea and somnolence, as well as an earlier return of bowel function (114). In most studies, use of ketorolac has been associated with a less frequent incidence of PONV than the opioid analgesics. As a result, patients tolerate oral fluids and are fit for discharge earlier than those receiving only opioid analgesics during the perioperative period. Of interest, ketorolac (30 mg q 6 h) was superior to a dilute local anesthetic infusion (bupivacaine 0.125%) in supplementing epidural PCA hydromorphone in patients undergoing thoracotomy procedures (115). Furthermore, it has been found that the injection of ketorolac (30 mg) at the incision site in combination with local anesthesia resulted in significantly less postoperative pain, a better quality of recovery, and earlier discharge compared with local anesthesia alone (116). In fact, there is evidence for both a peripheral and central analgesic action of NSAIDs (117). However, when ketorolac was substituted for or combined with fentanyl during minor gynecologic and laparoscopic procedures, the beneficial effects of the NSAID were reduced (118,119).

Using shock wave lithotripsy to evaluate the effect of NSAIDs on visceral pain, diclofenac produced only a marginal opioid-sparing effect (120). However, when diclofenac (1 mg/kg IV) was administered before arthroscopic surgery, it was associated with similar pain scores to fentanyl (1 μg/kg IV) (121). Preoperative diclofenac (50 mg) also decreased pain and the opioid analgesic requirements for 24 h after laparoscopic surgery (122). Similarly, preoperative administration of ketorolac to patients undergoing laparoscopic cholecystectomy (119) decreased postoperative opioid requirements and improved some ventilatory variables during the early postoperative period. A perioperative ketorolac infusion (2 mg/h) also improved the quality of postoperative pain relief after abdominal surgery (123). Compared to tramadol (100 mg IV), ketorolac (30 mg IV) produced comparable analgesia with a 68% decreased incidence of PONV after maxillofacial surgery (124). Of interest,

Table 3. Dosage Recommendations for Acute Pain and Duration of Action of COX-2 Inhibitors

Drug (dosage range)	Route of administration	Onset (min)	Duration (h)	Ratio COX-1/2 activity	Key issues
Celecoxib (200–400 mg)	PO	30–50	4–8	8	Sulfonamide allergy
Rofecoxib (25–50 mg)*	PO	30–50	12–24	35	Leg edema, hypertension
Paracoxib (20–40 mg)†	IM/IV	10–15	6–12	30	Wound infections
Valdecoxib (20–40 mg)	PO	30–40	6–12	30	Steven's-Johnson syndrome
Etoricoxib (60–90 mg)	PO	20–30	≥24	106	Not known

COX-1/2 = Cyclooxygenase-1/2 receptor binding ratio.
* Withdrawn from the market because of cardiovascular complications associated with long-term use; † Intravenous prodrug of valdecoxib (the active "analgesic" compound).
Adapted from White (4).

diclofenac (1 mg/kg) is alleged to be a more cost-effective alternative to ketorolac (0.5 mg/kg) (125,126).

When diclofenac was administered preoperatively to pediatric patients, the incidence of restlessness and the incidence of crying, as well as the postoperative opioid requirements, were less than in acetaminophen-treated patients (127). Similarly, oral ketorolac (1 mg/kg) was superior to small-dose acetaminophen (10 mg/kg) in children undergoing bilateral myringotomy procedures (128). In children undergoing inguinal hernia repair (129), ketorolac (1 mg/kg IV) compared favorably with caudal bupivacaine 0.2% with respect to pain control and postoperative side effects. In addition, ketorolac-treated children had an improved recovery profile, including less vomiting, shorter times to voiding and ambulation, and earlier discharge home. Intraoperative administration of ketorolac as an adjuvant to general anesthesia in pediatric patients provided postoperative analgesia comparable to morphine with less PONV (130). When ketorolac or morphine is administered for pain control in pediatric patients, ketorolac-induced analgesia developed more slowly but lasted longer (131).

Oral or rectal administration of NSAIDs is also effective and less costly in the prophylactic management of surgical pain (132). For example, when oral naproxen was administered before laparoscopic surgery, postoperative pain scores, opioid requirements, and time to discharge were significantly reduced (133). Furthermore, premedication with oral ibuprofen (800 mg) was associated with superior postoperative analgesia and less nausea compared with fentanyl (75 μg IV) after laparoscopic surgery (134). However, the more important role for oral NSAIDs may be in the postdischarge period. Ibuprofen liquogel (400 mg po) was significantly more effective than celecoxib (200 mg po) in treating pain after oral surgery (135). Ibuprofen (5 mg/kg po) compared favorably to rofecoxib (0.625 mg/kg po) for minimizing postoperative pain when used in combination with acetaminophen (20 mg/kg) before tonsillectomy procedures (136). When used as part of a multimodal analgesic technique consisting of alfentanil, lidocaine, and ketorolac (137), oral ibuprofen (800 mg q 8h) was equianalgesic to paracetamol 800 mg in combination with codeine 60 mg (q 8h) during the first 72 h after discharge, and resulted in better global patient satisfaction and less constipation than opioid-containing oral analgesics. Ibuprofen (400 or 600 mg po) appears to produce comparable analgesia to the combination of tramadol (75–112.5 mg) and acetaminophen (650 or 975 mg) for acute postoperative pain relief (138). To achieve the optimal benefit of using NSAIDs in the perioperative period, these compounds should be continued during the postdischarge period as part of a preventative pain management strategy (98).

Despite the obvious benefits of using NSAIDs in the perioperative period, controversy still exists regarding their use because of the potential for gastrointestinal mucosal damage and renal tubular and platelet dysfunction (139). Although some studies have found increased blood loss and risk of reoperation when ketorolac was administered to children undergoing tonsillectomy procedures (140,141), a recent systematic review of the literature suggested that the evidence supporting an increase of bleeding was equivocal at best (142).

COX-2 Inhibitors

In an effort to minimize the potential for operative site bleeding complications, as well as gastrointestinal damage, associated with the classic nonselective NSAIDs such as ketorolac and diclofenac, the more highly selective COX-2 inhibitors are increasingly being used as non-opioid adjuvants for minimizing pain during the perioperative period (Table 3) (143). Early clinical studies in surgical patients evaluated the use of celecoxib, rofecoxib, and valdecoxib as preventative analgesics when administered for oral premedication (144–148). Rofecoxib (50 mg po) produced more effective and sustained analgesia compared with celecoxib (200 mg po) after spinal surgery (144). Celecoxib (200 mg po) was equivalent to acetaminophen (2 g po) when administered before otolaryngologic operations (145). However, the analgesic efficacy of celecoxib is

dose-related and 400 mg is the currently recommended dose for prevention of acute pain (146). Rofecoxib (50 mg po) produced significantly more effective analgesia than acetaminophen (2 g po) and the pain relief was more sustained in the postdischarge period (147). Premedication with rofecoxib also facilitated recovery by reducing postoperative pain and improving the quality of recovery from the patient's perspective (148). It has also been suggested that the long-acting rofecoxib is more cost-effective than celecoxib in the perioperative period (149). In one study (143), a single preoperative dose of rofecoxib, 25–50 mg po, produced a 44%–59% reduction in the PCA morphine requirement after major abdominal surgery (150). However, clinical studies suggest a more sustained benefit can be achieved when the drug is administered both before and after surgery (148,151). The recent withdrawal of rofecoxib from the market by its manufacturer because of an increased risk of cardiovascular side effects after prolonged use (>16 mo) has led investigators to begin re-evaluating other COX-2 inhibitors in the perioperative period.

Valdecoxib has been introduced recently for the prevention of postoperative pain, with doses of 20–40 mg reducing the opioid requirement by 25%–50% after elective surgery (152,153). In patients undergoing oral surgery and bunionectomy, premedication with valdecoxib 40 mg appears to produce the optimal analgesic effect in the postoperative period (152). Valdecoxib is as rapidly acting and effective as oxycodone in combination with acetaminophen but has a longer duration of action and fewer side effects when used for the management of pain after oral surgery. Valdecoxib (40 mg po) was alleged to be even more effective than rofecoxib, 50 mg po, in treating pain after oral surgery (154).

A parenterally active COX-2 inhibitor, parecoxib (a prodrug which is rapidly converted to valdecoxib), has been investigated as an alternative to the parenteral NSAIDs (155–157). However, to achieve equianalgesia with the IV prodrug, a larger dose may be required compared with the orally active drug valdecoxib. Parecoxib is similar pharmacokinetically to both celecoxib and valdecoxib. Preliminary studies suggested that parecoxib (40–80 mg IV), was as effective and longer-acting than ketorolac (30 mg IV) in reducing pain after oral (158) and laparotomy surgery (159). Both preoperative and postoperative administration of this COX-2 inhibitor resulted in significant opioid-sparing effects, reduced adverse effects, and improved quality of recovery and patient satisfaction with postoperative pain management (152,160). Unfortunately, one study in patients undergoing cardiac surgery suggested that perioperative use of parecoxib and valdecoxib as part of a 14-day analgesic treatment regimen increased adverse events, including sternal wound infections (161). Another recent study found that although parecoxib, 40 mg IV, was given at induction of anesthesia, it was less effective than ketorolac, 30 mg IV, after tonsillectomy procedures (141). A new more highly-selective COX-2 inhibitor, etoricoxib (120 mg po), provided rapid and long-lasting pain relief after dental surgery (162). A recent study also suggested that etoricoxib was associated with fewer side effects than a standard opioid-containing oral analgesic. Current evidence suggests that the newer COX-2 inhibitors appear to offer minimal advantages over the first-generation COX-2 inhibitors and the nonselective NSAIDs (163,164).

In addition to the growing controversy regarding the potential adverse cardiovascular risks of the COX-2 inhibitors, many orthopedic surgeons are also concerned about the negative influence of these compounds (as well as the traditional NSAIDs) on bone growth (165,166). As COX-2 activity appears to play an important role in bone healing (167–169), some orthopedic surgeons have recommended that these drugs be avoided in the early postoperative period (164,165). Because the effect on bone growth is dose-dependent and reversible (166), COX-2 inhibitors should only be used for 3–5 d in the early postoperative period. Although several review articles on the COX-2 inhibitors have recently been published (163,170–172), the question remains as to whether these compounds truly overcome the perceived *limitations* of the nonselective NSAIDs (173).

Acetaminophen (Paracetamol)

Of the non-opioid analgesics, acetaminophen (also known as paracetamol) is perhaps the safest and most cost-effective non-opioid analgesic when it is administered in analgesic dosages. Although both parenteral and rectal acetaminophen produce analgesic effects in the postoperative period, concurrent use with a NSAID is superior to acetaminophen alone (145,147). The addition of acetaminophen, 1 g every 4 h, to PCA morphine improved the quality of pain relief and patient satisfaction after major orthopedic procedures (174). Although Watcha et al. (128) reported minimal analgesic-sparing effects after a 10 mg/kg oral dose of acetaminophen, Rusy et al. (140) found that a larger dose (35 mg/kg pr) was as effective as ketorolac (1 mg/kg IV) in reducing pain after tonsillectomy procedures and was associated with less postoperative bleeding. Subsequently, Korpela et al. (175) demonstrated that the opioid-sparing effect of rectal acetaminophen was dose-related up to 60 mg/kg. The optimal dosing regimen for acetaminophen in children appears to consist of a preoperative initial dose of

30–40 mg/kg followed by a maintenance dose of 15–20 mg/kg every 6–8 h during the early postoperative period (176). In adults, acetaminophen 2 g orally was equivalent to celecoxib 200 mg but less effective than celecoxib 400 mg, rofecoxib 50 mg, or ketoprofen 150 mg in preventing pain after ambulatory surgery (145–147).

An IV formulation of a prodrug of acetaminophen, propacetamol, has been administered to adults as an alternative to ketorolac in the perioperative period (177,178). Propacetamol reduced PCA morphine consumption by 22%–46% in patients undergoing major orthopedic surgery (179,180). However, in patients undergoing cardiac surgery, propacetamol (2 g IV every 6 h for 3 d) failed to enhance analgesia, decrease opioid usage, or reduce adverse side effects in the postoperative period (181). Propacetamol has become a popular adjuvant to opioid analgesics for postoperative pain control in Europe; however, this drug may soon be replaced when an investigational IV formulation of acetaminophen becomes available for clinical use (182). Rectal acetaminophen (1.3 g) has also been successfully used as an adjuvant to NSAIDs and local anesthetics as part of a multimodal fast-tracking surgery recovery protocol (183). Given the adverse effects associated with both NSAIDs and COX-2 inhibitors in patients with preexisting cardiovascular disease, acetaminophen may assume a greater role in postoperative pain management in the future (184).

NMDA Antagonists

Ketamine is a unique IV anesthetic with analgesic-like properties that has been used for both induction and maintenance of anesthesia (185), as well as an analgesic adjuvant during local anesthesia (186,187). As a result of its well known side-effect profile (Table 4), ketamine fell into disfavor in the late 1980s. However, adjunctive use of small doses of ketamine (0.1–0.2 mg/kg IV) appear to be associated with a opioid-sparing effects and a less frequent incidence of adverse events and greater patient and physician acceptance (188). Several studies have described the use of small-dose ketamine in combination with local anesthetics and/or opioid analgesics (189–199). However, when ketamine (1 mg/mL) was combined with morphine (1 mg/mL) for PCA after major abdominal surgery, it did not significantly improve pain relief and was associated with increased side effects (e.g., vivid dreaming) compared with the opioid alone (191). One study (192) supports use of a PCA morphine-ketamine combination in a 1:1 ratio with a lockout interval of 8 min for pain control after major orthopedic procedures. Further studies are obviously needed to clarify ketamine's role as a supplemental analgesic.

Table 4. Potential Side Effects of Opioid and Non-Opioid Analgesic Drugs

- Opioid analgesics
  - respiratory and cardiovascular depression
  - nausea, vomiting, retching and ileus
  - urinary hesitancy and retention
  - pruritus and skin rash
  - sedation and dizziness
  - tolerance and dependence
- Local anesthetics
  - residual motor weakness
  - peripheral nerve irritation
  - cardiac arrhythmias
  - allergic reactions
  - sympathomimetic effects (due to vasoconstrictors)
- Nonsteroidal antiinflammatory drugs and COX-2 inhibitors
  - operative-site bleeding
  - gastrointestinal bleeding
  - renal tubular dysfunction
  - allergic reactions (e.g., Steven's-Johnson syndrome)
  - bronchospasm
  - hypertension
  - pedal edema
- Acetaminophen
  - gastrointestinal upset
  - sweating
  - hepatotoxicity
  - agranulocytosis
- Ketamine and NMDA antagonists
  - hypertension
  - diplopia and nystagmus
  - dizziness and confusion
  - cardiac arrhythmias
  - nausea and vomiting
  - psychomimetic reactions
- Alpha-2 adrenergic agonists
  - sedation
  - dizziness
  - hypotension
  - bradycardia
- Miscellaneous drugs
  - somnolence, dizziness and peripheral edema (gabapentin)
  - nausea and vomiting (neostigmine)
  - muscle weakness and sedation (magnesium)
- Nonpharmacologic techniques
  - skin irritation and erythema
  - cutaneous discomfort

NMDA = *N*-methyl-D-aspartate; COX-2 = cyclooxygenase-2.
Adapted from White (4).

Administration of ketamine, 4–18 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in combination with propofol, 30–90 $\mu g \cdot kg^{-1} \cdot min^{-1}$, obviated the respiratory depression produced by commonly used sedative-opioid combinations while producing positive mood effects after surgery, and it may even provide for an earlier recovery of cognitive function (186,187). In addition, a single bolus dose of ketamine, 0.1–0.15 mg/kg IV, during surgery has been reported to produce significant opioid-sparing effects after painful

orthopedic and intraabdominal procedures without increasing the incidence of side effects (194–200). Ketamine (0.1 mg/kg IM) reduced swallowing-evoked pain after tonsillectomy procedures in children receiving a multimodal analgesic regimen (198). Small doses of epidural ketamine (20–30 mg) enhanced epidural morphine-induced analgesia after major upper abdominal surgery (199). Although it was alleged that ketamine possesses preemptive analgesic effects as a result of its ability to inhibit central NMDA receptors (200), well controlled clinical studies have failed to demonstrate significant preemptive analgesic effects (201,202). Interestingly, a modest dose of ketamine (250 μg/kg) after surgery was alleged to improve analgesia in the presence of opioid-resistant pain (203). Acute tolerance to opioid-induced analgesia leading to long-lasting hyperalgesia may be prevented by repeat doses of this NMDA antagonist (204).

Small-doses of the S(+) and R(-) isomers of ketamine have been administered both IV and epidurally in an effort to decrease injury-induced hyperalgesia. Although S(+) ketamine (0.5 mg/kg IV followed by 0.125–1 μg/kg/min) failed to improve pain control after arthroscopic knee surgery (205), epidural S(+) ketamine (0.25 mg/kg) enhanced ropivacaine-induced analgesia after total knee arthroplasty (206). Interestingly, transdermal nitroglycerin (5 mg) has been alleged to enhance the spinal analgesia produced by epidural S(+) ketamine (0.1–0.2 mg/kg) (207). Consistent with an early comparative clinical study involving the ketamine isomers (208). R(-) ketamine (1 mg/kg IV) produced only a short-lasting analgesic effect in the postoperative period (209).

Dextromethorphan, another NMDA receptor antagonist that inhibits wind-up and NMDA-mediated nociceptive responses in dorsal horn neurons, has been alleged to enhance opioid, local anesthetic and NSAID-induced analgesia. Premedication with dextromethorphan (150 mg po) reduced the PCA morphine requirement in the early postoperative period after abdominal hysterectomy procedures but failed to produce prolonged beneficial effects on wound hyperalgesia (210). In patients undergoing laparoscopic cholecystectomy or inguinal herniorrhaphy procedures, dextromethorphan (90 mg po) improved well-being and reduced analgesic consumption, pain intensity and sedation, as well as thermal-induced hyperalgesia (211). Preincisional administration of dextromethorphan, 40–120 mg IM, provided some evidence of preemptive analgesia in patients undergoing laparoscopic cholecystectomy and upper abdominal surgery (212,213). Perioperative dextromethorphan (40–90 mg IM) reduced the opioid requirement and/or improved pain control after modified radical mastectomy (214). Interestingly, in patients undergoing knee surgery, dextromethorphan (200 mg q 8 h) failed to significantly improve pain management (215). Compared with ibuprofen (400 mg po), dextromethorphan (120 mg po) was significantly less effective in providing postoperative analgesia and was associated with increased nausea in the preoperative period (216). In patients undergoing knee replacement surgery with epidural anesthesia, dextromethorphan (40 mg IM) also failed to produce any preemptive analgesic effect but did enhance pain control in the postoperative period (217).

Other NMDA antagonists are being actively investigated in the perioperative setting. Preoperative amantadine, 200 mg IV, failed to enhance postoperative analgesia in patients undergoing abdominal hysterectomy procedures (218). However, a more recent study reports that perioperative amantadine reduced PCA morphine requirement after radical prostatectomy surgery (219). Further clinical studies are clearly needed to better define the role of noncompetitive NMDA receptor antagonists in the perioperative setting.

Alpha-2 Adrenergic Agonists

The α_2-adrenergic agonists, clonidine and dexmedetomidine, produce significant anesthetic and analgesic-sparing effects. Premedication with oral and transdermal clonidine decreased the PCA-morphine requirement 50% after radical prostatectomy surgery (220). Clonidine also improved and prolonged central neuraxis (221,222) and peripheral nerve blocks (223) when administered as part of multimodal analgesic regimens. For example, epidural infusion of clonidine in combination with ropivacaine improved analgesia after major abdominal surgery in children (224). Adding intrathecal clonidine (0.075 mg) to local anesthesia provided excellent analgesia for up to 8 h after urologic surgery (225). Although clonidine, 4 μg/kg IV over 20 min, failed to reduce PCA morphine requirement after lower abdominal surgery in adults, it did reduce pain, nausea, and vomiting while improving patient satisfaction with their pain relief (226). However, when used to treat postoperative pain, clonidine (0.3 mg IV) was apparently ineffective (227).

Dexmedetomidine is a pure α_2-agonist that also reduces postoperative pain and opioid analgesic requirement (228). However, its use was associated with increased postoperative sedation and bradycardia. When used for premedication before IV regional anesthesia (229), dexmedetomidine (1 μg/kg IV) reduced patient anxiety, sympathoadrenal responses, and intraoperative opioid analgesic requirement. Compared with propofol (75 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dexmedetomidine (1 μg/kg followed by 0.4–0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) had a slower onset and offset of sedation but was associated with improved analgesia and reduced morphine use in the postoperative period

(230). Administration of dexmedetomidine, 1 μg/kg followed by 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$, was also associated with a 66% reduction in PCA morphine use in the early postoperative period after major inpatient surgery (231).

Miscellaneous Non-Opioid Compounds

A diverse array of non-opioid pharmacologic compounds used during the perioperative period, such as adenosine (232,233), droperidol (234), magnesium (235), neostigmine (236), and gabapentin (237,238), have been alleged to possess analgesic-sparing properties. Although the analgesic-sparing effects of these compounds have not been extensively evaluated and their use for acute postoperative pain management is considered investigational, the preliminary findings are nonetheless intriguing. For example, use of an adenosine infusion as an alternative to an opioid analgesic (remifentanil) for controlling acute autonomic responses during lower abdominal surgery resulted in a significant reduction in both postoperative pain scores and the requirement for opioid analgesics (232).

Gabapentin (a structural analog of gamma-aminobutyric acid) is an anticonvulsant that has proven useful in the treatment of chronic neuropathic pain and may also be a useful adjuvant in the management of acute postoperative pain (237–242). For example, premedication with gabapentin (1.2 g po) reduced postoperative analgesic requirement significantly without increasing side effects (237). When gabapentin (1.2 g) was continued for 10 d after breast surgery (238), it reduced the postoperative opioid analgesic requirement and movement-related pain; however, the overall incidence of chronic pain was unaffected. Recent studies by Dierking et al. (239), Turan et al. (240), and Rorarius et al. (241) suggested that the improvement in postoperative pain control with gabapentin was not necessarily associated with a decrease in opioid-related side effects. Pregabalin, a related compound, has also been reported to possess analgesic potential comparable to that of ibuprofen in treating acute dental pain (242). This review article discussed the potential role of gabapentin and pregabalin in "protective premedication."

Magnesium, a divalent cation, is also alleged to possess antinociceptive effects. For example, Kara et al. (235) reported that perioperative magnesium (30 mg/kg IV followed by an infusion of 0.5 g/h) yielded a significant reduction in the postoperative analgesic requirement after abdominal hysterectomy. A bolus dose of magnesium (50 mg/kg IV) at induction of anesthesia also led to improved pain control and better patient satisfaction with less opioid medication after major orthopedic surgery (243). However, magnesium 50 mg/kg IV failed to produce opioid-sparing effects after open cholecystectomy procedures (244). In addition, a non-opioid multimodal analgesic regimen that included magnesium produced comparable postoperative pain relief with fewer side effects than fentanyl in obese patients undergoing gastric bypass surgery (245). However, other investigators have failed to demonstrate a beneficial effect of magnesium (30–50 mg/kg followed by 10–15 $mg \cdot kg^{-1} \cdot h^{-1}$) with respect to reducing postoperative pain or the need for opioid analgesics (246). Of interest, intrathecal magnesium was reported to prolong fentanyl analgesia (247).

Neostigmine, a cholinesterase inhibitor, has been reported to possess analgesic properties when doses of 10–200 μg were administered in the subarachnoid or epidural spaces (236,248). Although peripherally administered neostigmine failed to produce postoperative analgesia, epidurally administered neostigmine (1 μg/kg) produced more than 5 h of pain relief after knee surgery (249). Neostigmine (10 μg/kg) also enhanced epidural local analgesia (250). Both epidural (60 μg) and spinal (1–5 μg) neostigmine enhanced morphine-induced neuraxial analgesia (251–254). In patients undergoing knee replacement surgery with intrathecal bupivacaine, adjunctive use of neostigmine (50 μg) was alleged to produce better postoperative analgesia than morphine (300 μg) (255). In addition, transdermal nitroglycerin enhanced spinal neostigmine-induced postoperative analgesia without increasing perioperative side effects (256). However, epidural neostigmine (75–300 μg) alone produced only modest analgesia after cesarean delivery (257). The primary adverse effects associated with neuraxial neostigmine appear to be mild sedation (257) and PONV (15%–30%) (237,253).

Cannabinoids have been reported to reduce hyperalgesia and drug-induced allodynia. However, clinical studies have failed to demonstrate any evidence of postoperative analgesia (258,259). A new antiinflammatory drug, inositol triphosphate, reduced postoperative pain and the need for opioid analgesics after cholecystectomy surgery (260). However, additional well controlled clinical trials are needed with all of these novel adjunctive drugs.

Nonpharmacologic Techniques

Nonpharmacologic "electroanalgesic" techniques such as transcutaneous electrical nerve stimulation (TENS), acupuncture-like transcutaneous electrical nerve stimulation, and percutaneous neuromodulation therapy can also be useful adjuvants to pharmacologic compounds in the management of acute postoperative pain (261). Given the inherent side effects

produced by both opioid and non-opioid analgesics (Table 4), it is possible that the use of nonpharmacologic approaches will assume a more prominent role in the future management of acute postoperative pain (262).

Clinical studies suggest that electroanalgesia can reduce opioid analgesic requirements up to 60% after surgery (263,264). In addition to reducing pain and the need for oral analgesics, Jensen et al. (265) reported a more rapid recovery of joint mobility after arthroscopic knee surgery. When used as an adjuvant to pharmacologic analgesia, TENS reduced the intensity of exercise-induced pain and facilitated ambulation after abdominal surgery (266). In reviewing the medical literature, Carroll et al. (267) found conflicting results regarding the effect of TENS on the requirement for opioid analgesic medication and the quality of postoperative pain relief. Studies suggest that the location, intensity, timing, and frequency of electrical stimulation are all important variables influencing the efficacy of electroanalgesics therapies (263,264,268). More recent studies have confirmed the importance of these variables in achieving improved pain relief with TENS therapy (269).

Of interest, simple (mechanical) intradermal needles placed in the paravertebral region before abdominal surgery reduced postoperative pain and the opioid analgesic requirement as well as PONV (270). However, a "minute sphere"-induced acupressure technique (in which 1-mm stainless steel spheres are applied at known analgesic acupoints) failed to relieve pain after major abdominal surgery (271). Other nonpharmacologic approaches that have been used as analgesic adjuvants in the perioperative period include cryoanalgesia (272), ultrasound (273), and laser stimulation (274), as well as hypnotherapy. However, well controlled clinical studies are needed to establish benefits of these nonpharmacologic modalities on postoperative pain and patient outcomes after surgery.

Summary

As more extensive and painful operations (e.g., laparoscopic cholecystectomy, adrenalectomy, and nephrectomy procedures, as well as prostatectomy, laminectomy, shoulder and knee reconstructions, hysterectomy) are performed on an outpatient or short-stay basis, the use of multimodal perioperative analgesic regimens involving non-opioid analgesic therapies will likely assume an increasingly important role in facilitating the recovery process and improving patient satisfaction (4). Pavlin et al. (275) confirmed the importance of postoperative pain on recovery after ambulatory surgery. Moderate-to-severe pain prolonged recovery room stay by 40–80 min. Use of local anesthetics and NSAIDs decreased pain scores and facilitated an earlier discharge home. Additional outcome studies are needed to validate the beneficial effect of these non-opioid therapeutic approaches with respect to important recovery variables (e.g., resumption of normal activities, dietary intake, bowel function, return to work). Although many factors other than pain *per se* must be controlled to minimize postoperative morbidity and facilitate the recovery process (1), pain remains a major concern of all patients undergoing elective surgical procedures (276).

Opioid analgesics continue to play an important role in the management of moderate-to-severe pain after surgical procedures. However, adjunctive use of non-opioid analgesics will likely assume a greater role as minimally invasive ("key hole") surgery continues to expand (2,4). In addition to the local anesthetics, NSAIDs, COX-2 inhibitors, acetaminophen, ketamine, dextromethorphan, α-2 agonists, gabapentin, magnesium, and neostigmine may all prove to be useful adjuncts in the management of postoperative pain in the future. Adjunctive use of droperidol (234) and glucocorticoid steroids (277,278) also appear to provide beneficial effects in the postoperative period. Use of analgesic drug combinations with differing mechanisms of action as part of a multimodal regimen will provide additive (or even synergistic) effects with respect to improving pain control, reducing the need for opioid analgesics, and facilitating the recovery process (279). Safer, simpler, and less costly analgesic drug delivery systems are needed to provide cost-effective pain relief in the postdischarge period as more major surgery is performed on an ambulatory (or short-stay) basis in the future. In introducing new therapeutic modalities for pain management, it is important to carefully consider the risk:benefit ratio (280).

In conclusion, the optimal non-opioid analgesic technique for postoperative pain management would not only reduce pain scores and enhance patient satisfaction but also facilitate earlier mobilization and rehabilitation by reducing pain-related complications after surgery. Recent evidence suggests that this goal can be best achieved by using a combination of preemptive techniques involving both central and peripheral-acting analgesic drugs and devices.

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