Role of Non-Opioid Analgesic Techniques in the Management of Pain After Ambulatory Surgery

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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, the effective treatment of acute postsurgical pain still poses unique challenges for practitioners (1). An increasing number and complexity of operations are being performed on an outpatient basis where the use of conventional opioid-based IV patient-controlled analgesia (PCA) and central neuroaxial (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).

The 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 it 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 complications (e.g., ventilatory depression, drowsiness and sedation, postoperative nausea and vomiting [PONV], pruritus, urinary retention, ileus, constipation) that can contribute to a delayed hospital discharge (4). In addition, 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 or the development of acute tolerance (5). Use of 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.

This refresher course lecture will discuss recent evidence supporting the use of non-opioid analgesic drugs and techniques during the perioperative period for facilitating the recovery process after ambulatory surgery.

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 (4). When administered before the start of surgery, these simple techniques can also decrease the anesthetic and analgesic requirements during the operation and reduce the need for opioid-containing analgesics in the postoperative period. More effective pain relief in the early postoperative period as a result of the residual sensory block produced by local anesthetics facilitates the recovery process 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.

Although local anesthetic supplementation clearly 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 or intermittent perfusion 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. The efficacy of local anesthetic infusion systems is clearly enhanced when the catheter is placed at the facial level or in the vicinity of 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. Similarly, a continuous intraclavicular brachial plexus block provides highly effective pain control after discharge in patients undergoing shoulder surgery. Although continuous local anesthetic infusions with concomitant PCA capability appear to be superior to a continuous infusion alone for prolonging nerve blocks, many patients elect not to use the PCA function on their electronic pumps.

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When using continuous local anesthetic infusions, the 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 as well as the accuracy and consistency of the pumps. The use of disposable, non-electronic infusion systems may offer advantages over the electronic pump because their simplicity minimizes the need for troubleshooting. However, the accuracy of the infusion rate of non-electronic pumps can vary over time. Temperature changes also influence the infusion rate of the elastomeric pumps, whereas battery life is a limiting factor for the electronic pumps. With these catheter delivery systems the risk of infection appears to be low, although the incidence of bacterial colonization of the catheter is high. Patient satisfaction and comfort when using these delivery systems outside the hospital was also high, and more than 90% of the patients were comfortable removing the catheter at home. Finally, combining local anesthetic infusion techniques with other analgesic modalities as part of multimodal (or "balanced") analgesic therapy further improves pain control throughout the perioperative period.

Nonsteroidal Anti-inflammatory Drugs

Early clinical studies suggested that parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) possessed analgesic properties comparable to those of opioid analgesics without opioid-related side effects. Compared with the partial opioid agonist tramadol, diclofenac produced better postoperative pain relief with fewer side effects after cardiac surgery. When administered as adjuvants during outpatient anesthesia, ketorolac was associated with improved postoperative analgesia and patient comfort compared with fentanyl and the partial opioid agonist, dezocine. Other investigators reported that ketorolac provided similar postoperative pain relief to that of fentanyl but was associated with less nausea and somnolence and an earlier return of bowel function. In most studies, use of ketorolac was found to be associated with a lower incidence of PONV than opioid compounds. As a result, patients tolerated oral fluids and were judged "fit for discharge" earlier than those receiving only opioid analgesics during the perioperative period. Of interest, ketorolac (30 mg q 6h) was superior to a dilute local anesthetic infusion (bupivacaine 0.125%) in supplementing epidural PCA opioid analgesia in patients undergoing thoracotomy procedures. Furthermore, it has been found that the administration of ketorolac (30 mg) at the incision site in combination with local anesthesia resulted in considerably less postoperative pain, a better quality of recovery, and earlier discharge than local anesthesia alone. Of interest, diclofenac (1 mg/kg) is alleged to be a more cost-effective alternative to ketorolac (0.5 mg/kg).

Oral or rectal administration of NSAIDs is also effective and less costly in the prophylactic management of surgical pain. For example, when oral naproxen was administered before laparoscopic surgery, postoperative pain scores, opioid requirements, and time to discharge were reduced (13). Furthermore, premedication with oral ibuprofen (800 mg) was associated with superior postoperative analgesia and less nausea than fentanyl (75 μg IV) after laparoscopic surgery. However, the more important role for oral NSAIDs may be in the postdischarge period. Ibuprofen liquigel (400 mg PO) was more effective than celecoxib (200 mg PO) in the treatment of pain after oral surgery. When used as part of a multimodal analgesic technique consisting of alfentanil, lidocaine, and ketorolac, 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 the opioid-containing oral analgesic. Ibuprofen (400 or 600 mg PO) appears to produce comparable analgesia to combination tramadol (75–112.5 mg) and acetaminophen (650 or 975 mg) for acute postoperative pain relief. 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.

Cyclooxygenase-2 Inhibitors

In an effort to minimize the potential for operative site bleeding complications and gastrointestinal damage associated with the classical nonselective NSAIDs such as ketorolac and diclofenac, the more highly selective cyclooxygenase-2 (COX-2) inhibitors are increasingly being utilized as non-opioid adjuvants for minimizing pain during the perioperative period. The early clinical studies in surgical patients evaluated the use of celecoxib, rofecoxib, and valdecoxib for preventative analgesia when administered for oral premedication. Rofecoxib (50 mg PO) produces more effective and sustained analgesia than celecoxib (200 mg PO) after spinal surgery. Celecoxib (200 mg PO) was equivalent to acetaminophen (2 g PO) when administered before otolaryngologic operations. However, the analgesic efficacy of celecoxib is dose-related; 400 mg is the currently recommended dose for prevention of acute pain. Rofecoxib (50 mg PO) produced more effective analgesia than acetaminophen (2 g PO) and the pain relief was more sustained in the postdischarge period. Premedication with rofecoxib also facilitated the recovery process by reducing postoperative pain

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and improving the quality of recovery from the patient's perspective.

Valdecoxib has been introduced more recently for the prevention of postoperative pain, with doses of 20–40 mg producing a 25%–50% reduction in the postoperative opioid requirement after major surgery. In patients undergoing oral surgery and bunionectomy procedures, premedication with valdecoxib 40 mg appears to produce the optimal analgesic effect in the postoperative period. Valdecoxib is as rapidly acting and efficacious 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.

A parenterally active COX-2 inhibitor, parecoxib (a pro-drug for valdecoxib), has been introduced as an alternative to ketorolac and diclofenac. Parecoxib is similar, both pharmacokinetically and pharmacodynamically, to celecoxib and valdecoxib. Parecoxib (40–80 mg IV) was reported to be as effective and longer-acting than ketorolac (30 mg IV) in reducing pain after oral and laparotomy surgery. Both preoperative and postoperative administration of this COX-2 inhibitor resulted in opioid-sparing effects, reduced adverse effects, and improved the quality of recovery and patient satisfaction with postoperative pain management. Unfortunately, a recent study suggested that perioperative use of parecoxib and valdecoxib as part of a 14-day analgesic treatment regimen increased postoperative sternal wound infections (15). Controversy also exists regarding the potential for cardiovascular complications following short-term administration of the highly selective COX-2 inhibitors. Additional comparative clinical studies are clearly needed to define better the advantages of this parenteral COX-2 inhibitor over existing COX-2 drugs and nonselective NSAIDs in the perioperative period (16). Although several review articles on the COX-2 inhibitors have recently been published in the medical literature, the question remains as to whether these novel compounds overcome the perceived *limitations* of the nonselective NSAIDs.

Acetaminophen (Paracetamol)

Of the non-opioid analgesics, acetaminophen (also known as paracetamol) is potentially one of the safest and least costly drugs. Acetaminophen is a viable alternative to the NSAIDs because of its lower cost and favorable side effect profile. Although both parenteral and rectal acetaminophen produce analgesic effects in the postoperative period, concurrent use with an NSAID is superior to acetaminophen alone. The addition of acetaminophen, 1 g q 4h, to PCA morphine improved the quality of pain relief and patient satisfaction after major orthopedic procedures. When administered in an appropriate dose, acetaminophen can be a useful adjuvant during the perioperative period and compared favorably with the NSAIDs in children. Although Watcha et al. (17) reported minimal analgesic-sparing effects after a 10 mg/kg oral dose of acetaminophen, Rusy et al. (18) found that a larger dose (35 mg/kg PR) was as effective as ketorolac (1 mg/kg IV) in reducing pain after tonsillectomy and was associated with less postoperative bleeding. Subsequently, Korpela et al. (19) 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 loading 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. In adults, acetaminophen 2 g PO 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.

An IV formulation of acetaminophen known as propacetamol has been administered to adults as an alternative to ketorolac in the perioperative period. However, in patients undergoing cardiac surgery, propacetamol (2 g IV q 6h for 3 d) failed to enhance analgesia, decrease opioid usage, or reduce adverse side effects in the postoperative period. Propacetamol is an injectable prodrug that is rapidly metabolized to acetaminophen. However, it will probably be replaced by an IV formulation of acetaminophen. Although the future role of this non-opioid analgesic in adults during the perioperative period is yet to be determined, rectal acetaminophen (1.3 g) has been successfully utilized as an adjuvant to NSAIDs and local anesthetics as part of a multimodal fast-tracking laparoscopic surgery recovery protocol.

Ketamine and Its Isomers

Ketamine is a unique IV anesthetic with analgesic-like properties that has been used for both induction and maintenance of anesthesia and as an analgesic adjuvant during local anesthesia. As a result of its well-known side effect profile, ketamine fell into disfavor in the early 1980s. However, adjunctive use of so-called small doses of ketamine (0.1–0.2 mg/kg IV) appear to be associated with a lower incidence of adverse events and greater patient and physician acceptance. Several studies have described the use of low-dose ketamine in combination with local anesthetics and/or opioid analgesics.

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 this combination may even provide for an earlier recovery of

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cognitive function. Ketamine (0.1 mg/kg IM) reduced swallowing-evoked pain after tonsillectomy procedures in children receiving a multimodal analgesic regimen. Small-doses of epidural ketamine (20–30 mg) were found to enhance epidural morphine-induced analgesia after major upper abdominal surgery. Although it was alleged that ketamine possesses preemptive analgesic effects (as a result of its ability to inhibit central *N*-methyl-D-aspartate receptors), well-controlled clinical studies have failed to demonstrate preemptive analgesic effects. Interestingly, a modest dose of ketamine (250 μg/kg) after surgery was alleged to improve analgesia in the presence of opioid-resistant pain. Acute tolerance to opioid-induced analgesia leading to long-lasting hyperalgesia may be prevented by repeat doses of this *N*-methyl-D-aspartate antagonist.

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 $\mu g \cdot kg^{-1} \cdot min^{-1}$) failed to improve pain control after arthroscopic knee surgery, epidural S(+) ketamine (0.25 mg/kg) enhanced ropivacaine-induced analgesia after total knee arthroscopy. Interestingly, transdermal nitroglycerin (5 mg) has been alleged to enhance the spinal analgesia produced by epidural S(+) ketamine (0.1–0.2 mg/kg). Consistent with an early comparative clinical study involving the ketamine isomers, R(-) ketamine (1 mg/kg IV) produced only a short-lasting analgesic effect in the postoperative period.

Alpha-2 Adrenergic Agonists

The α_2-adrenergic agonists, clonidine and dexmedetomidine, produce anesthetic and analgesic sparing effects. For example, oral-transdermal clonidine administered perioperatively produced a 50% decrease in the PCA morphine requirement after radical prostatectomy. Clonidine has also been found to improve and prolong central neuroaxis analgesia, peripheral nerve blocks, and intraarticular analgesia when administered as part of multimodal analgesic regimens. For example, an epidural infusion of clonidine in combination with ropivacaine improved analgesia after major abdominal surgery in children. The addition of intrathecal clonidine (0.075 mg) to local anesthesia provided excellent analgesia for up to 8 h after urologic surgery.

Dexmedetomidine is a pure α_2-agonist that also reduces postoperative pain and opioid analgesic requirement (20). However, its use was associated with increased postoperative sedation and bradycardia. When used for premedication before IV regional anesthesia, dexmedetomidine (1 μg/kg IV) reduced patient anxiety, sympathoadrenal responses, and the 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$) had a slower onset and offset of sedation but was associated with improved analgesia and reduced morphine use in the postoperative period.

Nonpharmacological Techniques

Nonpharmacological "electroanalgesic" techniques (e.g., transcutaneous electrical nerve stimulation [TENS], acupuncture-like transcutaneous electrical nerve stimulation [ALTENS], and percutaneous neuromodulation therapy [PNT]) can also be useful adjuvants to pharmacologic compounds in the management of acute postoperative pain (21). Given the inherent side effects produced by both opioid and non-opioid analgesics, it is possible that nonpharmacologic approaches will assume a more prominent role in the future management of acute postoperative pain. Clinical studies suggest that electroanalgesia can produce up to a 60% reduction in the opioid analgesic requirement after surgery. In addition to reducing pain and the need for oral analgesics, use of electroanalgesia can provide for a more rapid recovery of joint mobility after arthroscopic knee 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, and 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. (22) have recently confirmed the importance of postoperative pain on recovery after ambulatory surgery. Moderate-to-severe pain prolonged the recovery room stay by 40–80 min. Use of local anesthetics and NSAIDs decreased pain scores and facilitated earlier discharge home. Additional outcome studies are needed to validate the beneficial effect of these non-opioid therapeutic approaches with respect to important recovery parameters (e.g., resumption of normal activities [e.g., dietary intake, bowel function] and 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 (23).

Opioid analgesics will continue to play an important role in the management of moderate-to-severe pain after surgical procedures. However, the adjunctive use of non-opioid analgesics will likely assume a

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greater role as minimally invasive ("key hole") surgery continues to expand in the future (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 (24). Adjunctive use of droperidol and glucocorticoid steroids (25,26) also appears 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 (9–11,27,28). Non-pharmacological approaches (e.g., TENS, TAES) can be helpful in improving pain control and decreasing postoperative emetic sequelae (29). Finally, safer, simpler, and less costly analgesic drug delivery systems are needed to provide cost-effective pain relief in the post-discharge period as more "major" surgery is performed on an ambulatory (or short-stay) basis in the future.

In conclusion, the optimal 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 (30). 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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