Recent Management Advances in Acute Postoperative Pain

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Abstract

Introduction: Acute postoperative pain remains a major problem, with both undertreatment and overtreatment leading to serious consequences, including increased risk of persistent postoperative pain, impaired rehabilitation, increased length of stay and/or hospital readmission, and adverse events related to excessive analgesic use, such as oversedation. New analgesic medications and techniques have been introduced that target the preoperative, intraoperative, and postoperative periods to better manage acute postoperative pain, with improvements in analgesic efficacy and safety over more traditional pain management approaches. This review provides an overview of these new analgesic medications and techniques. Specific topics that are discussed include the use of preoperative nonsteroidal anti-inflammatory drugs, anxiolytics, and anticonvulsants; intraoperative approaches such as neuraxial analgesia, continuous local anesthetic wound infusion, transversus abdominis plane block, extended-release epidural morphine, intravenous acetaminophen, and intravenous ketamine; and postoperative use of intravenous ibuprofen, new opioids (eg, tapentadol) or opioid formulations (morphine–oxycodone), and patient-controlled analgesia.

Conclusion: New, targeted, analgesic medications and techniques may provide a safer and more effective approach to the management of acute postoperative pain than traditional approaches such as postoperative oral analgesics.

Key Words: acute pain, analgesia, preoperative, intraoperative, postoperative, perioperative, review

INTRODUCTION

An estimated 25 million inpatient surgeries and an additional 35 million ambulatory surgeries are performed annually in the USA.1,2 Greater than 80% of surgical patients experience postoperative pain, and 39% experience “severe” to “extreme” postoperative pain.3 The mismanagement of postoperative pain, whether undertreatment or overtreatment, is associated with a variety of negative consequences, including cardiac alterations and increased risk of myocardial ischemia or infarction, thromboembolic and pulmonary complications, immune alterations, increased risk of persistent postoperative pain, impaired rehabilitation, increased length of stay and/or hospital readmission, decreased quality of life, and adverse events related to excessive analgesic use.4-8

The consequences of overtreatment are often overlooked but can be life-threatening. Indeed, an observational study of surgical patients found high rates of analgesic-induced oversedation in the first 12 postoperative hours, with dangerous levels of sedation occurring in 72.7% of patients on patient-controlled analgesia (PCA).4 A chart review of trauma center site surveys reported to the American College of Surgeons...
Committee on Trauma as part of their verification process identified excessive use of analgesics as a direct factor in 13 of 1,655 deaths (0.7%) from 1994 through 1998 and in 32 of 867 deaths (3.6%) from 2000 through 2004.

A variety of new analgesic medications and techniques have been introduced to more effectively manage acute postoperative pain during the preoperative, intraoperative, and postoperative periods, all of which may contribute to the development of acute postoperative pain. This review will focus on new analgesic medications and techniques targeted for use during these periods for the management of acute postoperative pain.

PAIN MANAGEMENT APPROACHES TARGETED AT THE PREOPERATIVE PERIOD

Interventions targeted at the preoperative period are increasingly common and often are used for “preemptive analgesia” or as part of a “preventive analgesia” regimen. Preemptive analgesia involves the preoperative administration of an analgesic so that it is active during surgery. Administration at this time should reduce the consequences of afferent nociceptive neurotransmission arising from the surgery itself, thereby decreasing postoperative pain.

In contrast, preventive analgesia involves a broader approach to postoperative pain management, in that the goal is to prevent central sensitization by blocking the neural transmission of all noxious perioperative stimuli arising from the time of incision until wound healing, which then should decrease postoperative pain and analgesic use, as well as the risk of persistent postoperative pain. Preventive analgesia aims to minimize central sensitization by blocking the consequences of all perioperative noxious stimuli, not just those arising from the surgery itself; it is slowly replacing preemptive analgesia as the more encompassing approach to postoperative pain management.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, ketorolac, etoricoxib, celecoxib), anxiolytics (eg, midazolam), and anticonvulsants (eg, gabapentin, pregabalin) have been studied in the preoperative setting. What follows is a review of the current literature on use of these classes of drugs before surgery.

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics, antipyretics, and anti-inflammatory agents that act by inhibiting the enzyme cyclooxygenase, which is responsible for the biosynthesis of prostaglandins. Inflammation and nerve injury secondary to surgery may independently trigger postoperative pain and result in central sensitization and persistent postoperative pain.

A recent, randomized, placebo-controlled, clinical trial comparing a single preoperative dose of the selective cyclooxygenase (COX)-2 inhibitors etoricoxib and celecoxib in patients undergoing arthroscopic anterior cruciate ligament reconstruction under spinal anesthesia found that patients receiving etoricoxib (but not celecoxib) had significantly less intense pain for the first 8 hours. However, the 2 treatment groups did not differ from the placebo group in time to first dose or amount of postoperative analgesic used (recorded at 48 hours), or in pain intensity from 12 to 48 hours. These findings suggest limited efficacy of etoricoxib as a preemptive analgesic.

A meta-analysis of the effects of a single perioperative (preoperative or intraoperative) intravenous or intramuscular dose of ketorolac (30 mg or 60 mg) for postoperative pain found that ketorolac reduced pain at rest in the early (0 to 4 hours) but not late (24 hours) postoperative period, with a greater analgesic effect following intramuscular administration than following intravenous administration. The 60-mg dose of ketorolac also reduced postoperative opioid use and nausea and vomiting. These findings suggest that a single, intramuscular dose of ketorolac may be effective as a preemptive analgesic during the preoperative or intraoperative periods.

Theoretically, NSAIDs with a longer elimination half-life should be more effective in reducing postoperative pain when administered preoperatively. For individual patients, the efficacy of NSAIDs should be weighed against the risk of serious adverse events affecting the gastrointestinal, renal, and cardiovascular systems, although the risk of these adverse events should be decreased when only a single preoperative dose is administered. A systematic review of the efficacy and safety of selective COX-2 inhibitors in the perioperative setting identified a consistent opioid-sparing effect of COX-2 inhibitors, which should further decrease analgesic complications by reducing the risk of opioid-related adverse events such as respiratory depression.

Although the available data are conflicting, clinicians should be aware of the potential for NSAIDs to impair bone healing, and NSAIDs should be avoided in patients at high risk of impairments in bone healing, particularly for surgeries that directly involve the bone such as arthroplasty.
Anxiolytics

Anxiety is common prior to surgery and is associated with poor outcomes, including severe postoperative pain.22 Researchers have explored the use of anxiolytics for managing anxiety and pain, with positive results.

Midazolam is a benzodiazepine that is commonly administered to decrease preoperative anxiety and produce anesthesia.23 A recent, randomized, double-blind, clinical trial compared the efficacy and safety of preoperative diclofenac (an NSAID) with or without midazolam in patients undergoing hernia repair surgery under general anesthesia.24 The results showed that compared with patients receiving diclofenac alone, patients receiving preoperative midazolam in combination with diclofenac experienced significantly less postoperative pain in the first 3 postoperative hours (6-point Verbal Rating Scale [VRS] score, median [range]: 1.4 [0 to 4] vs. 2.4 [1 to 5]; P < 0.001). Thus, preoperative midazolam can enhance the analgesic effects of diclofenac. The combination of midazolam and diclofenac also resulted in significantly less nausea/vomiting, but with a greater degree of sedation and hypotension than that observed with diclofenac alone.24

Whether midazolam’s analgesic effect is secondary to its anxiolytic effect is unclear, although intrathecal administration of midazolam to rats has been shown to produce analgesic effects by actions on the GABA_A receptor complex.25 A randomized case–control study of human patients undergoing lower abdominal, gynecological, or orthopedic surgery under spinal anesthesia found that intrathecal midazolam significantly increased the time to first use of postoperative analgesics and prolonged the duration of sensory blockade, without increasing the incidence of sedation.26

Anticonvulsants

Gabapentin and pregabalin are anticonvulsant drugs that act at the α_2δ subunit of presynaptic, voltage-gated, Ca^2+ channels.27,28 The efficacy of preoperative gabapentin and pregabalin in decreasing postoperative pain has been investigated in randomized clinical trials and in meta-analyses.

A randomized, placebo-controlled, clinical trial of the effects of a single preoperative dose (600 mg) of gabapentin in patients undergoing cesarean delivery under spinal anesthesia found a reduction in pain scores on movement and at rest in the gabapentin group compared with the placebo group, although postoperative opioid consumption was similar in the two groups.29 Severe sedation was greater in the gabapentin group, but no significant group difference was found in the incidence of postoperative nausea and vomiting, or in neonatal outcomes.29

A meta-analysis of the effects of gabapentin in randomized, controlled, clinical trials found that preoperative gabapentin produced a significant decrease in postoperative analgesic consumption.30 In this review, preoperative gabapentin was found to produce a significant decrease in vomiting (but not nausea); however, its use was associated with a significant increase in sedation and dizziness.30

A randomized, double-blind, placebo-controlled, clinical trial of the effects of 2 perioperative doses of pregabalin (75 mg each, administered 1 hour before surgery and 12 hours after the first dose) in patients undergoing mastectomy under general anesthesia showed that compared with patients receiving placebo, patients receiving pregabalin experienced less pain at rest over the first 48 postoperative hours (48-hour 11-point Verbal Numerical Rating Scale [VNRS] score at rest, median [range]: 0 [0 to 4] for pregabalin vs. 2 [1 to 5] for placebo; P < 0.001) and with arm abduction for 1 week after surgery (1-week VNRS score, median [range]: 1 [0 to 4] for pregabalin vs. 3 [0 to 5] for placebo; P < 0.001), with an exception of the 6-hour postoperative time point).31 There was no group difference in sedation, postoperative nausea and vomiting, or postoperative analgesic use.31

A meta-analysis of the effects of pregabalin in randomized, placebo-controlled, clinical trials found that perioperative (preoperative or pre/postoperative) administration of pregabalin produced a significant decrease in postoperative pain at rest (Hedges’ g effect size: −0.31; 95% confidence interval [CI]: −0.50, −0.12) and with movement (Hedges’ g effect size: −0.27; 95% CI: −0.50, −0.05), and in postoperative analgesic use (Hedges’ g effect size: −0.32; 95% CI: −0.49, −0.14 for studies with no group difference in pain scores at rest; Hedges’ g effect size: −0.98; 95% CI: −1.58, −0.38 for studies with a group difference in pain scores at rest).32 However, these effects were accompanied by an increase in dizziness or lightheadedness and visual disturbances.32

PAIN MANAGEMENT APPROACHES TARGETED AT THE INTRAOPERATIVE PERIOD

Intraoperative analgesic techniques and formulations include neuraxial analgesia, continuous local anesthetic
wound infusion, transversus abdominis plane (TAP) block, extended-release epidural morphine (EREM), intravenous acetaminophen, and intravenous ketamine.

**Neuraxial Analgesia**

Neuraxial analgesia involves local administration of an anesthetic and/or opioids into the neuraxial space of the spinal cord.

Neuraxial analgesia aims to reduce the afferent transmission of nociceptive signaling and to block the development of central sensitization. Neuraxial analgesic techniques include spinal or epidural analgesia, regional nerve blocks targeting the surgical field, peripheral nerve blocks targeting the nerve innervating the surgical field, and local nerve blocks targeting local tissue in the surgical field. While these techniques are effective at reducing postoperative pain, they are not without complications. Nerve injuries, in particular, are common after neuraxial analgesia, although severe or disabling neurological complications are rare.

Ultrasound guidance during peripheral nerve block has received increased attention as a method to not only improve the accuracy of nerve localization and needle placement but also to improve postoperative pain. A systematic review of randomized, controlled, clinical trials on the effects of ultrasound guidance during peripheral nerve block found little evidence of improvement in postoperative pain management, although the available data were limited to the 23 trials that met the inclusion criteria for review.

The conflicting evidence regarding the benefit of ultrasound guidance might be related, at least in part, to the level of experience of the anesthetist. Indeed, the use of ultrasound guidance requires extensive training and routine practice. Anesthetists must fully understand ultrasound theory and equipment and the relevant anatomy. Furthermore, adequate training programs must be in place to ensure that anesthetists develop and maintain the competencies required to successfully perform the technique.

**Continuous Local Anesthetic Wound Infusion**

Continuous infusion of local anesthetic into the surgical field was introduced as a simple alternative to neuraxial or peripheral nerve blockade for the management of postoperative pain. When infused into the surgical field, local anesthetics produce analgesic effects by direct inhibition of the local inflammatory response to surgical trauma. While local anesthetic wound infusion appears to provide better postoperative pain relief than placebo infusion, it is unclear whether it is superior to traditional neuraxial or peripheral nerve blockade.

A randomized, controlled, investigator-blind, clinical trial compared 48-hour continuous wound infusion of ropivacaine with bolus injections of epidural morphine administered every 12 hours for up to 48 hours in patients undergoing elective cesarean delivery and found that compared with patients receiving epidural morphine, patients receiving the continuous wound infusion had significantly lower pain scores at rest over the first 48 postoperative hours (48-hour 11-point VNRS score, median [interquartile range, IQR]: 0 [0 to 0] vs. 2 [0 to 2]; \( P < 0.001 \)) and with movement over the first 6 postoperative hours (6-hour VNRS score, median [IQR]: 1 [0 to 4] vs. 5 [4 to 5]; \( P < 0.001 \)). Although there was no group difference in the use of rescue analgesics, the incidence of adverse events was significantly reduced in patients receiving the continuous wound infusion when compared with patients receiving epidural morphine.

In contrast, another randomized, placebo-controlled, clinical trial in patients undergoing elective cesarean delivery found that pain scores at rest (but not with walking) were significantly lower among patients receiving perioperative epidural boluses of levobupivacaine compared with patients receiving perioperative subfascial boluses of levobupivacaine. However, the group difference was apparent only for the first 4 postoperative hours, and it was attributed to a greater dose of local anesthetic administered in the epidural group than in the subfascial group.

Given the conflicting results, the available evidence suggests that wound infusion of local anesthetics may provide a useful approach to acute pain management with patients for whom neuraxial analgesia or peripheral nerve blockade is not an acceptable choice.

**TAP Block**

The TAP block was first described by Rafi and involves the injection of local anesthetics into the neurovascular plane of the abdominal wall. Interest in the use of the TAP block for acute pain management is growing. A systematic review and meta-analysis of the literature identified 7 randomized, double-blind, clinical trials and found that in 4 of the 7 trials, pain scores at rest and with motion were significantly decreased in the early
postoperative period (0 to 6 hours) among patients receiving the TAP block compared with those who did not. In 6 of the 7 trials, patients receiving the TAP block also consumed less postoperative morphine, and a meta-analysis confirmed the opioid-sparing effect of the TAP block.

Another meta-analysis of 4 randomized, placebo-controlled, clinical trials found that patients receiving the TAP block consumed less postoperative morphine and waited longer to request postoperative analgesia than patients who did not receive the TAP block. Postoperative pain scores measured at 6 and 24 hours were lower among patients who received the TAP block. However, these findings were not found in the postanesthesia care unit or at 2 hours. The incidence of postoperative nausea and vomiting did not differ between groups.

**EREM**

Extended-release epidural morphine (EREM) was approved in 2004 as a single-dose analgesic administered by epidural injection at the lumbar level for the treatment of pain following major surgery. EREM is administered immediately before surgery or after clamping the umbilical cord during cesarean delivery. The efficacy of EREM in the treatment of postoperative pain has been established, but the safety of EREM has been questioned.

A study using pooled data from 5 randomized clinical trials conducted between 1998 and 2003 compared the use of intravenous PCA with fentanyl or morphine in combination with epidural placebo, epidural morphine sulfate (5 mg), or EREM (5 to 30 mg) on postoperative pain after total hip arthroplasty, lower abdominal surgery, or cesarean delivery. The results showed that both epidural morphine and EREM decreased postoperative pain intensity at rest, and that a 10-mg dose of EREM produced a greater decrease in postoperative pain intensity with movement when compared with a 5-mg dose of epidural morphine, but the effect was limited to the first postoperative day. Postoperative PCA opioid use was lower with both epidural morphine and EREM, but a 10-mg dose of EREM produced a greater effect than a 5-mg dose of epidural morphine on postoperative day 2. There were no significant differences among the treatment groups in the incidence of respiratory depression, nausea, vomiting, pruritus, or urinary retention, except for a tendency for a greater incidence of adverse events with higher doses of EREM.

In contrast to the study discussed above, a meta-analysis of the effects of EREM (10 to 30 mg) versus intravenous PCA with opioids focused on postoperative respiratory depression and found that EREM, while effective at providing postoperative analgesia for up to 48 hours, was associated with a significantly higher risk of respiratory depression (odds ratio [OR]: 5.80, 95% CI: 1.05, 31.93; \( P = 0.04 \)).

In response to concerns related to respiratory depression after neuraxial opioid administration, the American Society of Anesthesiologists (ASA) developed practice guidelines for the use of neuraxial opioids in the perioperative setting. With regard to EREM, the guidelines recommend periodic monitoring for a minimum of 48 postoperative hours, with increased monitoring for patients at high risk of respiratory depression (eg, obese, pediatric, and geriatric patients). The ASA also noted that they are “equivocal regarding whether extended-release epidural morphine increases the occurrence of respiratory depression compared with either parenteral opioids or conventional (immediate release) epidural morphine.”

**Intravenous Acetaminophen**

An intravenous formulation of acetaminophen was approved in 2010 for the management of fever, mild to moderate pain, or moderate to severe pain with adjunctive opioids. A systematic review of randomized, placebo-controlled, clinical trials of the safety and efficacy of perioperative (primarily intraoperative) intravenous acetaminophen for the management of postoperative pain found that patients receiving perioperative intravenous acetaminophen had lower pain scores in 12 of 14 trials and less postoperative opioid use in 10 of 14 trials.

Another systematic review and meta-analysis found that patients receiving perioperative (intraoperative or postoperative) intravenous acetaminophen were more likely than patients receiving placebo to experience 50% pain relief and to have less opioid use over the first 4 to 6 postoperative hours, with no group difference in the overall incidence of adverse events.

**Intravenous Ketamine**

Ketamine is a hypnotic drug that is commonly used for induction of anesthesia, especially in pediatric patients, and acts by antagonizing the N-methyl-D-aspartate receptor. Ketamine has received increased interest in recent years as an analgesic for acute pain management.
A randomized, double-blind, placebo-controlled, clinical trial evaluated the effects of intravenous or subcutaneous infiltration of ketamine administered 15 minutes before incision in patients undergoing appendectomy under general anesthesia. The results showed that treatment with ketamine by either route of administration resulted in significantly lower pain scores in the postanesthesia care unit than with placebo, but that intravenous administration of ketamine provided greater long-term postoperative pain relief than subcutaneous administration of ketamine, with significantly lower pain scores up to 24 postoperative hours (24-hour 10-cm visual analog scale [VAS] score, mean ± SD: 1.7 ± 0.9 for intravenous ketamine, 4.0 ± 1.5 for subcutaneous ketamine, and 4.4 ± 0.7 for placebo; \( P < 0.001 \)). The incidence of adverse events (nausea, vomiting, or dizziness) did not differ between the three groups.

A systematic review and meta-analysis of the effects of perioperative (intraoperative or postoperative) intravenous ketamine on postoperative pain and analgesic use identified an opioid-sparing effect of ketamine, with the greatest effects observed with surgeries associated with greater postoperative pain, such as abdominal surgery, thoracic surgery, and orthopedic limb or spine surgery. Ketamine was associated with a decrease in postoperative pain scores in 37.5% of studies at early time points (30 minutes to 4 hours) and 25% of studies at later time points (24 to 72 hours). In terms of adverse events, ketamine increased the incidence of neuropsychiatric effects (e.g., hallucinations) and decreased the incidence of postoperative nausea and vomiting, but did not alter the incidence of sedation or other side effects.

**PAIN MANAGEMENT APPROACHES TARGETED AT THE POSTOPERATIVE PERIOD**

Traditional pharmacological approaches to pain management in the postoperative period include oral or intravenous administration of opioids and oral administration of acetaminophen or NSAIDs. These approaches are associated with a variety of adverse events, including respiratory depression, nausea and vomiting, pruritus, and constipation with opioids, and gastrointestinal injury, myocardial infarction or stroke, and acute renal failure with NSAIDs. Accidental overdose and death also is not uncommon after opioid use. New opioids, drug delivery approaches and systems, and PCA techniques have been developed to enhance the analgesic effects of NSAIDs and opioids and to minimize the risk of adverse events.

**Intravenous Ibuprofen**

An intravenous formulation of ibuprofen was approved in 2009 for use in adults for fever reduction and the management of mild to moderate pain or moderate to severe pain with adjunctive opioids. A randomized, multicenter, double-blind, placebo-controlled, clinical trial of intravenous ibuprofen (400 or 800 mg) in patients undergoing orthopedic or abdominal surgery found that compared with placebo, the intravenous administration of 800 mg ibuprofen at wound closure and every 6 hours thereafter resulted in a significant decrease in morphine consumption (intent-to-treat [ITT] population, 24-hour morphine consumption, adjusted least squares mean ± standard error [SE]: 190.6 ± 13.1 mg vs. 223.0 ± 13.8 mg; \( P = 0.030 \)), patient-reported pain scores at rest (ITT population, 12- to 24-hour 100-mm VAS score, adjusted least squares mean ± SE: 32.6 ± 2.4 vs. 42.5 ± 2.6; \( P < 0.001 \)), and with movement (ITT population, 12- to 24-hour VAS score, adjusted least squares mean ± SE: 48.6 ± 2.6 vs. 58.8 ± 2.8; \( P < 0.001 \)) over the first 24 postoperative hours. A 400-mg intravenous dose of ibuprofen was less effective. In terms of adverse events, nausea and pyrexia were significantly less common among patients receiving intravenous ibuprofen than among patients receiving placebo, but dizziness was significantly more common among patients receiving the 800-mg dose of intravenous ibuprofen.

A recent review of clinical trials on the efficacy and tolerability of intravenous ibuprofen in hospitalized adult patients concluded that 800 mg of intravenous ibuprofen every 6 hours after surgery was efficacious as an adjunct to morphine and as a morphine-sparing agent. The same review further concluded that intravenous ibuprofen is generally well tolerated, with the most common adverse events being dizziness, headache, nausea, vomiting, flatulence, hemorrhage, and urinary retention.

Another review article focused on dosing strategies related to the pharmacokinetics and pharmacodynamics of intravenous ibuprofen. The authors concluded from their analysis that a rapid intravenous infusion of ibuprofen would provide a more rapid and reliable onset of analgesia than is typically achieved with the more common 30- to 60-minute infusion protocols.
New Opioids and Opioid Formulations

New opioids and opioid formulations are being developed with unique pharmacodynamic profiles that retain the analgesic effects of opioids but minimize the adverse events associated with traditional opioids, such as morphine, hydrocodone, and fentanyl.

Tapentadol is a novel, centrally acting, μ-opioid agonist, and norepinephrine reuptake inhibitor that is approved for the treatment of moderate to severe pain.\(^{62,63}\) Two oral formulations are available: tapentadol hydrochloride for acute pain, and extended-release tapentadol for chronic pain.\(^{62,63}\) A review of clinical trials of the safety and efficacy of tapentadol for the treatment of pain after bunionectomy found that tapentadol has similar efficacy to pure μ-opioid agonists but with fewer opioid-related gastrointestinal adverse events.\(^{64}\) New clinical trials are needed to determine whether tapentadol is safe and effective in the treatment of postoperative pain after other types of surgery.

A new drug application (NDA) has been submitted to the US Food and Drug Administration (FDA) for an oral dual-opioid formulation containing a fixed ratio (3:2) of morphine to oxycodone.\(^{65}\) A randomized, double-blind, placebo-controlled, clinical trial of morphine–oxycodone at ascending doses of 3/2, 6/4, 12/8, or 18/12 mg in patients who experienced moderate to severe pain after unilateral bunionectomy found that when compared with placebo, patients who received morphine–oxycodone had greater pain relief (responders: 65% for 18/12-mg morphine–oxycodone vs. 36% for placebo; \(P = 0.003\)) and required less supplemental analgesia (600-mg ibuprofen tablets per 24 hours, mean ± SE: 2.0 ± 0.40 for 18/12-mg morphine–oxycodone vs. 3.3 ± 0.31 for placebo; exact \(P\) value not reported) over the first 48 postoperative hours.\(^{66}\) Nausea was the most common adverse event among patients receiving morphine–oxycodone, occurring in 38% to 65% of patients. Somnolence was the least common adverse event, occurring in 2% to 8% of patients receiving morphine–oxycodone, but few patients discontinued study participation due to adverse events.\(^{66}\)

Another randomized, double-blind, parallel-treatment, multicenter, clinical trial in patients undergoing unilateral bunionectomy demonstrated dose-dependent analgesic effects of morphine–oxycodone that were comparable to or greater than those achieved with equivalent doses of morphine or oxycodone alone.\(^{67}\) The mean (SE) sum of pain intensity difference over the first 24 hours was superior with the morphine–oxycodone combination product (12/8 mg, 54.3 [7.5]) compared with each component alone (12 mg morphine, 28.5 [8.1]; \(P = 0.009\); 8 mg oxycodone, 35.7 [7.5]; \(P = 0.037\)), and when compared with a lower dosage strength (6/4 mg, 30.0 [7.8]; \(P = 0.011\)). The incidence of nausea and vomiting (the most common adverse events) was higher in patients receiving morphine–oxycodone than in patients receiving morphine or morphine-equivalent doses of oxycodone alone (nausea, 76.5% vs. 58.6% and 50.0%; vomiting, 52.9% vs. 24.1% and 26.5%; 12/8 mg combination vs. 12 mg morphine and 8 mg oxycodone, respectively).\(^{67}\)

PCA. Patient-controlled analgesia (PCA) is increasingly recognized as a safe and effective method of postoperative pain management, with the potential to improve postoperative pain management by minimizing the frequency of analgesic gaps.\(^{68}\) Intravenous PCA with opioids and patient-controlled epidural analgesia (PCEA) with opioids and/or local anesthetics are the most common methods of PCA.\(^{68}\) Less common approaches for PCA include patient-controlled regional anesthesia (PCRA), patient-controlled intranasal analgesia (PCINA), patient-controlled transdermal analgesia (PCTA), and patient-controlled sublingual analgesia (PCSA).

PCRA. Patient-controlled regional anesthesia (PCRA) typically involves the administration of a local anesthetic into the surgical incision, intra-articular tissue, or perineural site.\(^{68}\) A number of studies have demonstrated the safety and efficacy of PCRA, and increased attention has focused on the use of PCRA for postoperative care after ambulatory surgery. For instance, a randomized, multicenter, clinical trial compared perineural PCRA with ropivacaine (by continuous infusion or basal–bolus) with intravenous PCA with morphine for home care after ambulatory orthopedic surgery (acromioplasty or bunionectomy) under general anesthesia.\(^{69}\) The results showed that compared with patients receiving intravenous morphine PCA, patients receiving perineural PCRA with ropivacaine consumed significantly less supplemental ketoprofen (mean ± SD: 200 ± 100 mg for continuous ropivacaine infusion, 100 ± 100 mg for basal–bolus ropivacaine, and 500 ± 100 mg for intravenous morphine PCA; exact \(P\) value not reported) and experienced fewer drug-related adverse events, including nausea/vomiting, dizziness, and local vein inflammation, over 72 postoperative hours.\(^{69}\) Additionally, patients receiving perineural PCRA with ropivacaine (particularly by basal–bolus infusion) showed greater rehabilitation, including...
A patient-controlled intranasal formulation of ketorolac tromethamine was approved in 2010 for short-term (up to 5 days) management of moderate to moderately severe pain in adults requiring opioids. A randomized, double-blind, placebo-controlled, clinical trial examined the safety and efficacy of PCINA with ketorolac (10 or 30 mg) in patients undergoing major abdominal or orthopedic surgery under general anesthesia. Compared with patients receiving PCINA with placebo, patients receiving PCINA with 30-mg ketorolac consumed less morphine over the first 48 postoperative hours (mean ± standard error of the mean [SEM]; 61.4 ± 10.8 mg vs. 87.9 ± 9.4 mg; P = 0.0060) and had greater pain relief at 6 postoperative hours (Summed Pain Intensity Difference [SPID] score, mean ± SEM: 195.5 ± 12.1 vs. 130.6 ± 14.4; P = 0.0015). The incidence of adverse events was similar among the 3 groups, although patients receiving PCINA with 30-mg ketorolac were less likely than those receiving placebo to experience pyrexia or tachycardia. Nasal irritation was more common among patients receiving either dose of ketorolac. Similarly, another randomized, double-blind, placebo-controlled, clinical trial in patients undergoing major open abdominal surgery under general anesthesia found that patients receiving PCINA with ketorolac had greater pain relief over the first 30 postoperative hours than patients receiving PCINA with placebo (30-hour 100-mm VAS, least squares mean ± SE: 24.3 ± 1.5 vs. 29.5 ± 2.2; P = 0.037). Patients receiving PCINA with ketorolac also used less supplemental analgesia compared with patients receiving PCINA with placebo.

The overall incidence of adverse events was similar in the 2 groups. Nasal discomfort was more common among patients receiving PCINA with ketorolac than among those receiving placebo, but the difference was not significant. Although nasal irritation is common after PCINA with ketorolac, this approach appears to be useful in combination pharmacotherapy for postoperative pain.

PCINA. A patient-controlled intranasal formulation of ketorolac tromethamine was approved in 2010 for short-term (up to 5 days) management of moderate to moderately severe pain in adults requiring opioids. A randomized, double-blind, placebo-controlled, clinical trial compared the efficacy of perineural PCRA with ropivacaine, perineural PCRA with saline (placebo), and oral analgesics (unblinded control) for postoperative pain relief after ambulatory surgery for open carpal tunnel release under local anesthesia. Patients receiving PCRA with ropivacaine experienced greater pain relief than patients receiving PCRA with saline, and fewer patients receiving PCRA with ropivacaine required supplemental analgesics than patients receiving oral analgesics (24% vs. 73%; P = 0.001). The 3 groups did not differ in the rate of functional recovery, however. PCRA appears to provide safe and efficacious postoperative analgesia and may promote functional recovery after ambulatory surgery.

PCTA. The fentanyl iontophoretic transdermal system (fentanyl ITS) was approved in 2006 for the treatment of acute postoperative pain in adult inpatients requiring postoperative opioids. This PCTA system is not yet marketed in the USA or elsewhere, however, because new system features are under development. Fentanyl ITS was developed as an alternative to intravenous PCA, with a lower risk of intravenous PCA–related complications such as operating errors, mechanical pump errors, and intravenous catheter infections.

An open-label, multicenter, randomized, active-controlled, parallel-group, clinical trial compared the safety and efficacy of the fentanyl ITS with that of intravenous PCA with morphine in patients undergoing abdominal or pelvic surgery. A significantly greater proportion of patients receiving fentanyl ITS reported “excellent” postoperative pain control (50.0% vs. 40.2%; P = 0.039). In terms of pain scores, fentanyl ITS was equivalent to morphine intravenous PCA over the 72-hour study period. Further, patients in both groups consumed similar amounts of supplemental analgesics after the first 3 postoperative hours, and the incidence of opioid-related adverse events was similar in the 2 groups. While not superior to intravenous PCA with morphine, in terms of safety or efficacy, patients receiving fentanyl ITS were more likely to report greater ease-of-care scores, suggesting that fentanyl ITS may improve ease of care, perhaps by reducing the frequency of analgesic gaps.

A secondary subset analysis was conducted on data from a randomized, multicenter, clinical trial comparing the safety and efficacy of fentanyl ITS with that of intravenous PCA with morphine for postoperative pain relief after major abdominal or orthopedic surgery under general or spinal anesthesia. Although the analysis was qualitative, in general, the results demonstrated similar efficacy (evaluated by pain intensity scores, patient and investigator assessment, and supplemental analgesic use) for fentanyl ITS and intravenous PCA with morphine over the first 24 postoperative hours, regardless of type of surgery (spine, hip, knee, lower or upper abdominal, or pelvic), gender, ASA status (I or II), or type of anesthesia (spinal or general).
Across all subsets, the incidence of adverse events was largely similar among the 2 treatment groups. Application-site reactions did occur in up to half of patients receiving fentanyl ITS; however, most of these were mild or moderate and resolved without treatment.\(^7\)\(^7\) Fentanyl ITS may represent a comparable and potentially safer alternative to intravenous PCA with morphine for postoperative pain management.

**PCSA.** A new, patient-controlled, sublingual, sufentanil system (ARX-01 Sufentanil NanoTab PCA System; AcelRx Pharmaceuticals, Inc) is underdevelopment and designed to overcome the key disadvantages of intravenous PCA; namely, drug-related adverse events, infections of indwelling intravenous catheters, human programming errors related to the PCA pump, and excessive somnolence.\(^7\)\(^5\)\(^7\)\(^8\) Little published literature is available on this sufentanil PCSA system, although the company producing the product reports that in 3 multicenter, randomized, double-blind, placebo-controlled, Phase II, clinical trials, patients undergoing unilateral knee arthroplasty or major abdominal surgery experienced significantly less postoperative pain with the sufentanil PCSA system.\(^7\)\(^8\)

**CONCLUSION**

Many new analgesic medications and techniques have been developed that target the preoperative, intraoperative, or postoperative periods to reduce acute postoperative pain. These include preoperative use of NSAIDs, anxiolytics, and anticonvulsants; intraoperative use of neuraxial analgesia, continuous local anesthetic wound infusion, TAP block, EREM, intravenous acetaminophen, and intravenous ketamine; and postoperative use of intravenous ibuprofen, new opioids (eg, tapentadol) or opioid formulations (morphine–oxycodone), and PCA approaches (eg, PCRA, PCINA, PCTA, PCSA). Many of these analgesic medications and techniques have demonstrated analgesic superiority to placebo and comparable analgesic efficacy to traditional approaches, coupled with a reduction in adverse events. Several of the newer medications and techniques show potential to improve analgesia and minimize the risk of adverse events, although additional research is needed to establish their efficacy and safety profile. New targeted approaches to acute postoperative pain management may provide safer and more effective analgesia than traditional approaches such as postoperative oral analgesics.

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