▼ Review Articles

Patient-Controlled Drug Delivery for Acute Postoperative Pain Management: A Review of Current and Emerging Technologies

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Postoperative pain management has dramatically improved with the advent of patient-controlled analgesia (PCA) delivery. The optimal PCA system would encompass several key characteristics, including consistent efficacy across a number of surgeries; safety of both the analgesic drug delivered and the delivery system; ease of setup, maintenance, and administration; patient comfort during analgesic delivery; avoidance of analgesic gaps; minimal invasiveness; and it would be associated with high patient satisfaction. Existing PCA modalities (using intravenous or epidural routes) encompass some of these characteristics (e.g., they have demonstrated efficacy across a number of surgeries); however, they are limited by the need for an indwelling catheter and the time and resources required for system setup and use. Device programming-related medication errors by hospital staff are an unfortunate risk, and could lead to significant harm. New PCA technologies are on the horizon that address some of the limitations to existing modalities; however, the added complexity of these newer systems are a concern, and their benefits and drawbacks remain to be assessed. These technologies include "smart" intravenous PCA infusion pumps to improve the safety of analgesic administration; needle-free options, such as the fentanyl HCl iontophoretic transdermal system for transdermal delivery; and a number of PCA devices for intranasal delivery, as well as several new options for patient-controlled regional analgesia. This review will discuss the benefits and drawbacks of both existing and emerging PCA modalities in the context of the ideal PCA system, and provide a critical evaluation of their use in postoperative settings. *Reg Anesth Pain Med 2008;33:146-158.*

Key Words: Patient-controlled analgesia, PCA, Postoperative pain, Epidural analgesia, Regional analgesia, Iontophoresis.

The undermanagement of postoperative pain that persists in spite of guidelines issued by several professional organizations[1,2] and the availability of a variety of pain management technologies[3] suggest that these systems are either not as effective as they could be or that their use is not being fully optimized. Better methods of pain assessment and management should lead to improved overall outcomes, as unrelieved pain can result in psychological distress and serious physiologic effects that may result in potentially life-threatening postoperative complications.[4,5] Much remains to be done to ensure that pain management guidelines are implemented, and that currently available systems are used appropriately, so that postoperative pain is adequately controlled.

Barriers to effective postoperative pain management persist. Opioids are the most commonly used agents for postoperative pain management and yet the undertreatment of postoperative pain is attributed at least in part to concerns about opioid use, such as physician and patient fears of addiction and overdosage.[6] Some practitioners maintain that efforts to provide more aggressive pain management should be exercised with caution, as increased dosing may lead to dangerous levels of sedation if the patient is not closely monitored.[7] Additional factors that may hinder adequate pain management include discrepancies between patients' and physicians' perceptions of patient pain[8] and limitations on staff time.[9]

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Patient-controlled analgesia (PCA) modalities, most commonly intravenous (IV) PCA, address many of the safety and efficacy issues associated with opioid use in the postoperative period. Following the establishment of pain control via IV administration of one or more opioid bolus doses, PCA is used to sustain comfort, allowing the patient to self-administer enough drug to achieve a balance between analgesia and side effects.[10] Dosing is generally regulated by PCA pump settings that control the dose, frequency of dosing, a lockout period between dosing, and a maximum allowable dose per hour. In addition, overdosing is minimized by the physiologic effects of the drug resulting in a negative feedback loop—if a patient administers too much analgesic, they begin to experience sedation, thereby preventing further self-administration.[10]

PCA modalities may minimize the occurrence of analgesic gaps by providing immediate dosing upon patient activation of the system, thus providing more uniform analgesia and eliminating potentially painful waiting periods between patient requests for analgesia and drug administration, compared with traditional nurse- or physician-administered intermittent drug delivery methods (e.g., IV bolus injections and intramuscular [IM] injections). Patient-administered doses are also typically smaller than bolus doses administered by nurses, which may improve the side effect to benefit ratio.

Patient-controlled epidural analgesia (PCEA) is also commonly used in the postoperative setting, and often provides superior efficacy and lower analgesic dose requirements compared with IV PCA. PCEA allows patients to initiate epidural doses of opioid, local anesthetic, or a combination of both. PCEA using local anesthetics has been shown to minimize opioid consumption and may be beneficial in patients who are especially sensitive to opioid-related side effects.

Despite their many advantages, PCA modalities are not without limitations. PCA systems are inherently complex and require training of hospital staff and coordination of inter-departmental resources for system setup, use, and maintenance. Intravenous PCA and PCEA involve an invasive route of administration and necessitate use of indwelling catheters. PCA pumps may also be prone to device malfunctions and mechanical failures as well as programming errors. Furthermore, the physically cumbersome nature of some PCA systems may impede postoperative mobility, an integral component of patient recovery and rehabilitation. PCEA may be associated with an increased risk of hypotension and motor block compared with analgesia delivered by non-epidural routes, and concomitant anticoagulant therapy may confer a heightened risk of spinal hematoma. Thorough patient education prior to PCA use and careful patient monitoring during PCA use are essential to analgesic success, ensuring both safety and efficacy and overall satisfaction.

Table 1. Key Characteristics of an Optimal PCA System

- Provide adequate pain relief according to individual analgesic needs
- Provide acceptable safety and tolerability profile
- Provide high levels of patient satisfaction
- Encounter minimal technology-related complications

Abbreviation: PCA, patient-controlled analgesia.

To better assess both existing and emerging PCA modalities for postoperative pain management, key characteristics of an optimal PCA modality should first be established. The optimal PCA delivery system should demonstrate an acceptable efficacy and safety profile, provide high levels of patient satisfaction, and encounter minimal technology-related complications (Table 1). Other desirable characteristics include the minimization of analgesic gaps, ease of use by the patient and health care team, and compatibility with current clinical care (e.g., physical therapy, activities of daily living, antithrombotic therapy). Previous articles have reviewed the safety and efficacy of common PCA modalities.[11-13] However, an updated, comprehensive review that includes a discussion of the benefits and limitations to a wide variety of PCA drug delivery techniques is warranted. This review provides a comprehensive overview of current PCA modalities as well as those in development, allowing for a comparison of the different technologies. Intravenous PCA and PCEA will be discussed, along with new developments in patient-controlled regional analgesia (PCRA), patient-controlled intranasal analgesia (PCINA), and the fentanyl HCl iontophoretic transdermal system (ITS) (Table 2).

Intravenous Patient-Controlled Analgesia (IV PCA)

Introduced more than 20 years ago, IV PCA has since become an accepted standard of acute postoperative pain management. Upon patient initiation of an activation button that is attached by a cord to the PCA pump, a small dose of opioid, most commonly morphine, is delivered by an IV line to an indwelling catheter. Dosing is controlled by a staff-programmed PCA pump, which can be adjusted to vary the infusion rate and bolus volume according to individual analgesic needs. A lockout interval is enforced in order to prevent excessive dosing within a prescribed period of time.

As with all PCA modalities, IV PCA optimizes analgesic efficacy by allowing the patient to deter-

Table 2. Comparison of Patient-Controlled Modalities Used for the Management of Acute Postoperative Pain

Modality	Analgesic Used	Advantages	Disadvantages
IV PCA	Morphine Fentanyl Hydromorphone	• Rapid analgesia • No first-pass GI effect • Patient control • Programmable	• Invasive • Pump apparatus, tubing, and power cables may limit patient mobility • Extensive staff time and resources required for administration • Requires programming by staff • Potential for IV line occlusions, catheter infiltration, and programming and drug errors
PCEA	Opioids Local anesthetics Opioid/local anesthetic combinations	• Rapid analgesia • No first-pass GI effect • Patient control • Programmable	• Invasive • Pump apparatus, tubing, and power cables may limit patient mobility • Extensive staff time and resources required for administration • Requires programming by staff • Potential for tubing occlusions, catheter dislodgement, and programming and drug errors • Requires advanced skills for administration • Risk of epidural hematoma in patients receiving anticoagulant therapy • Significant failure rate (approximately 30%)
PCRA	Local anesthetics: Ropivacaine Bupivacaine	• No first-pass hepatic effect • No first-pass GI effect • Minimized systemic opioid requirements • Targeted analgesia • Patient control	• Technique generally limited to orthopedic surgery patients • Further development of PCRA pumps needed • Efficacy and safety needs further evaluation • Requires advanced skills to place perineural catheters
PCINA	Fentanyl Morphine Butorphanol	• Noninvasive • No first-pass GI effect • Rapid analgesia • No first-pass hepatic effect • Patient control	• Not appropriate for patients with sinus problems • Further development of PCINA devices needed
Fentanyl ITS	Fentanyl	• Noninvasive • Rapid analgesia • Convenient, small in size, no required cables or pump • No programming by hospital staff required • No first-pass GI effect • Limited time and resources required for administration • Patient control	• Not appropriate for patients with skin disorders or injuries that prevent application • Individualization of dosing limited to frequency of dosing

Abbreviations: GI, gastrointestinal; ITS, iontophoretic transdermal system; IV, intravenous; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PCINA, patient-controlled intranasal analgesia; PCRA, patient-controlled regional analgesia.

mine their analgesic need and dose accordingly, minimizing the peaks and troughs in serum concentrations associated with clinician-controlled analgesia. Intravenous PCA has a well-established record of efficacy, safety, and patient satisfaction.[10,14,15] A meta-analysis of 15 randomized, controlled clinical studies demonstrated that opioids administered by IV PCA conferred significantly greater analgesic efficacy (a mean additional benefit of 5.6 on a pain scale score of 0 to 100; $P = .006$) compared with conventional IM analgesia.[15] A comprehensive review of the efficacy of various postoperative pain management methods indicated that for IM opioid analgesia and opioid IV PCA, the percentages of patients experiencing moderate to severe pain 24 hours post-surgery were 67.2% and 35.8%, respectively.[16] A more recent meta-analysis evaluated 32 randomized, controlled trials comparing IV PCA with analgesia administered by the IM, IV, or subcutaneous (SC) routes.[14] Intravenous PCA demonstrated superior analgesic efficacy over opioid analgesia delivered by bolus IM, IV, and SC doses when all pain outcomes (pain intensity, pain relief, requirement for rescue medication) were combined; however, no differences in actual pain scores were noted.[14] In addition, differences in analgesic consumption and opioid-related side effects were negligible.

One consistent finding of the 2 meta-analyses, as well as other clinical studies, is that IV PCA is associated with high patient satisfaction,[14,15,17-19] an essential characteristic of an optimal PCA modality. Evidence also indicates that IV PCA reduces patient

morbidity compared with IM administration.[20,21] With regard to safety, adverse events encountered with IV PCA are generally those associated with opioid use, including nausea, vomiting, pruritus, constipation, sedation, and respiratory depression.[22] Among these adverse events, the most serious condition is respiratory depression, which may possibly lead to hypoxic injury as a result of opioid overdose.[23] A recent review of published data on the respiratory effects of acute postoperative pain management methods indicated that for patients receiving IV PCA, the mean incidence of respiratory depression ranged from 1.2% to 11.5%.[24]

Despite its demonstrated efficacy and safety in large patient populations, IV PCA is associated with potential complications related to the PCA modality itself, as well as to patient or operator interference that have the potential to result in serious medication errors.[10,25,26] One recent study,[27] evaluating the incidence and causes of IV PCA-related medical events documented within the Food and Drug Administration's Manufacturer and User Device Facility Experience (MAUDE) database from January 1, 2002, to December 31, 2003, revealed that out of 2,009 events, 1,590 were possibly related to device safety. Of the 131 events that were attributed to operator errors, 106 were associated with pump programming errors, 63 were associated with patient harm, and 6 were associated with patient death.[27]

Other drawbacks exist. Intravenous PCA may limit patient comfort and mobility by requiring patient attachment to the PCA pump, IV line, and pole. In fact, an audit of postoperative surgical patients revealed that 21% of patients who received IV PCA complained of restricted mobility.[28] Patients and caregivers also face the risk of needle-related injuries. Furthermore, substantial hospital staff time is required for training and operation of the PCA pump. Thus, while demonstrating an acceptable efficacy and safety profile and providing high levels of patient satisfaction, IV PCA is invasive, limits postoperative mobility, and is prone to device-related complications and programming errors. While IV PCA may be considered by many to be the standard of care for postoperative pain management, room for further improvement exists.

Fortunately, recent advances in "smart intravenous infusion pumps" equipped with integrated decision support software may help reduce the incidence of medication errors.[29,30] These smart pumps contain drug libraries and provide decision support during analgesic administration to prevent both excessive and inadequate dosing. In a prospective, randomized time-series trial involving the inpatient use of an IV PCA smart pump, the software was able to document serious medication errors, including near-misses and preventable adverse drug events.[29] Such technological innovations offer promise in the prevention of potentially deleterious programming errors.

Finally, another limitation of IV PCA is the pharmacoeconomic burden associated with partially used drug cassettes. Collectively, unused drugs discarded from IV PCA devices may add up to significant, unnecessary costs that could potentially be circumvented in the future with the implementation of newer, more innovative PCA modalities.

Patient-Controlled Epidural Analgesia (PCEA)

The epidural route of drug delivery (bolus injection, continuous infusion, PCEA) provides rapid analgesia and reduces the systemic exposure to opioids. Epidural analgesia is commonly administered to patients who have undergone thoracic, major abdominal, or orthopedic surgery, and are experiencing severe levels of pain. Opioids administered by the epidural route confer greater analgesic potency relative to equivalent doses of opioids administered parenterally.[8] Both opioids and local anesthetics are agents for epidural analgesia; the latter may be a better choice for patients exceptionally sensitive to opioid-related side effects. However, use of epidural local anesthetics is associated with a higher incidence of hypotension, motor block, and urinary retention, compared with use of opioids.[8]

Like IV PCA, PCEA allows patients to self-administer drug doses according to analgesic needs. Large observational studies have demonstrated that PCEA is safe and effective for postoperative use in hospital wards.[31,32] In a randomized, double-blind study evaluating the efficacy of bupivacaine-fentanyl administration by PCEA or continuous infusion in patients recovering from total knee arthroplasty, patients in the PCEA group consumed significantly less bupivacaine-fentanyl ($P < .001$) compared with those in the continuous infusion group.[33] No significant differences in the need for rescue opioid or the incidence of side effects were noted. Other studies also have shown that PCEA lowers analgesic requirements[34,35] compared with continuous epidural infusion. Another randomized, double-blind study investigated post-Cesarean analgesia with fentanyl PCEA or single-dose epidural morphine.[36] While pain relief, patient satisfaction with pain relief, and consumption of supplemental medication were similar between treatment groups, a smaller proportion of patients receiving fentanyl PCEA experienced pruritus ($P < .0125$) compared with those receiving single-dose epidural morphine.[36]

Results of a recent meta-analysis indicated that epidural analgesia delivered by either continuous infusion or PCEA provided superior analgesia compared with opioid IV PCA, regardless of chosen drug, epidural route, or pain outcome measure.[37] Additionally, continuous epidural infusion was associated with greater analgesic efficacy relative to PCEA for overall pain, pain at rest, and pain with activity. However, with regard to adverse events, continuous epidural infusion was associated with a higher incidence of nausea/vomiting, sedation, urinary retention, and motor block, but a lower incidence of pruritus compared with PCEA.[37] Overall results are in accordance with those of a previous meta-analysis, which also demonstrated superior efficacy of epidural analgesia (continuous infusion, PCEA, and repeated bolus dosing) over parenteral analgesia (continuous infusion, bolus dosing by IV, IM, or SC routes, and IV PCA).[38] Equally high levels of patient satisfaction have been reported for PCEA and IV PCA.[19]

A prospective study of PCEA with bupivacaine and fentanyl administered to 1,030 postoperative patients revealed the following incidences of adverse events: pruritus (16.7%), nausea (14.8%), sedation (13.2%), hypotension (6.8%), motor block (2.0%), and respiratory depression (0.3%).[31] Such side effects are the direct result of opioid and local anesthetic use. A recent meta-analysis compared PCEA with continuous epidural infusion for labor analgesia.[39] Results indicated that while both methods were safe for mother and newborn, PCEA was associated with fewer anesthetic interventions, lower consumption of local anesthetic, and less motor block, compared with continuous epidural infusion. Also, a recent study has shown that PCEA provides higher maternal satisfaction compared with epidural analgesia administered continuously.[35]

The epidural route of analgesic administration faces potential complications associated with indwelling epidural catheters, which have been shown to dislodge, kink, or migrate within the epidural space, resulting in a catheter failure rate as high as 17%.[40] The lumbar placement of epidural catheters is also associated with a higher frequency of motor impairment compared with thoracic placement.[40] Epidural analgesic methods also face the potential for postdural puncture, infection, accidental spinal cord injury, and backache.[41] Moreover, use of indwelling epidural catheter techniques may not be suitable for all orthopedic surgery patients receiving anticoagulants, because there may be a heightened risk of spinal hematoma.[42,43]

As with IV PCA, one of the potential limitations of PCEA is the reliance on a staff-programmed pump and skilled and qualified members of the hospital staff for administration. In general, epidural techniques require a greater level of expertise than IV-related procedures, as the insertion of a small catheter into the epidural space requires great precision and accuracy. Manual programming of the PCEA pump also introduces the risk of programming errors, which can lead to medication errors and potentially serious consequences.[26] Additionally, the optimal variables for delivery of PCEA, such as demand dose, lockout interval, and continuous or background infusion, have not been clearly established.[10]

Patient-Controlled Regional Analgesia (PCRA)

Patient-controlled regional analgesia (PCRA) encompasses a variety of techniques that provide effective postoperative pain relief without systemic exposure to opioids. Using PCRA, patients initiate the delivery of small doses of local anesthetics, most frequently ropivacaine or bupivacaine, via an indwelling catheter, which can be placed in different regions of the body, depending upon the type of surgery. In some cases, a combination of local anesthetic and opioid is administered. Infusions are controlled either by a staff-programmed electronic pump (similar to that used for IV PCA) or a disposable elastomeric pump. An elastomeric pump is a device that has a distensible bulb inside a protective bulb, with a built-in filling port, delivery tube, and bacterial filter.[44] Analgesia can be delivered directly into a surgical incision (incisional PCRA), intra-articular (IA) tissue (IA PCRA), or perineural site (perineural PCRA).

A number of placebo-controlled trials have demonstrated the efficacy and safety of incisional PCRA. Fredman and colleagues[45] assessed the analgesic efficacy of ropivacaine 0.2% versus sterile water (both delivered by elastomeric PCRA pump) for postoperative pain following Cesarean delivery. Patients receiving ropivacaine required less rescue morphine (2 ± 3 mg vs. 10 ± 5 mg, respectively; $P < .01$) and reported lower pain scores after coughing and leg raise ($P < .04$) compared with those receiving placebo.[45] Additionally, more patients receiving PCRA rated the treatment modality as "excellent" or "good" than those receiving placebo (21/25 vs. 12/25, respectively).

Zohar and colleagues[46] examined the use of an electronic PCRA infusion pump to administer either bupivacaine 0.25% or sterile water into the surgical incision following total abdominal hysterectomy with bilateral salpingo-oophorectomy. Patients receiving incisional PCRA with bupivacaine used less rescue analgesia (morphine and meperidine; $P <$

.001), reported less nausea ($P = .003$), and reported significantly higher patient satisfaction ($P = .04$) compared with those in the placebo group.[46]

In a separate study,[47] incisional PCRA with ropivacaine 0.5% via an elastomeric PCRA pump provided superior analgesia without major side effects compared with bolus infusion in patients recovering from arthroscopic subacromial decompression. In another study,[48] 80% of patients who had received incisional PCRA with bupivacaine or ropivacaine delivered by an elastomeric PCRA pump reported that they would use the treatment modality again.

The IA administration of opioids and local anesthetics (alone or in combination) is routinely utilized for joint anesthesia.[49,50] Studies evaluating IA PCRA are limited, as published data focus primarily on single-dose and continuous modes of IA administration. Vintar et al.[51] recently reported the results of a randomized, placebo-controlled trial evaluating the efficacy of ropivacaine/morphine (RM), ropivacaine/morphine/ketorolac (RMK), and saline for postoperative pain management following anterior cruciate ligament construction (ACLC). Patients self-initiated bolus doses of the analgesic mixture or saline solution via a Microject® PCA pump. While no significant differences in pain scores, side effects, and patient satisfaction were noted among the study groups, patients receiving RMK consumed significantly less rescue morphine per day compared with those receiving RM and placebo (RMK, 8 ± 8 mg; RM, 23 ± 20 mg; placebo, 46 ± 21 mg; $P < .001$).

During orthopedic surgery, patients may be administered a single-injection peripheral nerve block, which provides approximately 12 to 15 hours of analgesia.[52] To more adequately control acute pain following orthopedic surgery, continuous perineural local anesthetic infusions, or continuous peripheral nerve blocks, are frequently used to continue analgesia after initial postoperative regional neural blockades have resolved. Infusion sites for the administration of peripheral nerve blocks include the axillary brachial plexus,[53] interscalene brachial plexus,[52,54] lumbar plexus,[55] femoral nerve,[56] and sciatic nerve.[55]

Perineural PCRA allows patients to self-titrate local anesthetic peripheral nerve blocks to achieve comfort. In a randomized, double-blind, placebo-controlled study,[52] perineural PCRA with ropivacaine 0.2% in the interscalene brachial plexus was shown to provide pain control superior to placebo in outpatients after moderately painful orthopedic surgery of the shoulder. On the first postoperative day, patients receiving perineural PCRA with ropivacaine reported significantly reduced pain ($P < .001$), less oral opioid use ($P < .001$), and lower sleep disturbance scores ($P = .013$) compared with patients receiving placebo infusions.[52]

Other trials in ambulatory patients receiving perineural PCRA into the brachial plexus at home have demonstrated that treatment with either ropivacaine 0.125% or bupivacaine 0.125% provides effective analgesia without signs and symptoms of local anesthetic toxicity.[53] The incidence of side effects and technical problems was generally low, with the most common complaint being numbness of the fingers (6.9% of ropivacaine patients and 29.0% of bupivacaine patients). On the day after surgery, the percentage of patients who were "satisfied" or "very satisfied" was similar in the 2 groups (79% for ropivacaine and 83% for bupivacaine, respectively). The majority of patients (87%) in both groups stated that they would want the same treatment after future surgical procedures.[53]

Recent studies have indicated that perineural PCRA results in equivalent or superior analgesic efficacy with lower total anesthetic consumption compared with continuous infusion.[56-60] Singelyn et al.[61] reported that following open shoulder surgery, interscalene brachial plexus analgesia administered by continuous basal infusion coupled with PCRA doses resulted in better analgesic efficacy compared with continuous infusion alone.

In a multicenter, randomized trial,[62] perineural ropivacaine administered by continuous infusion or PCRA was compared with patient-controlled IV morphine in patients recovering from ambulatory orthopedic surgery. Patients were discharged with disposable elastomeric pumps capable of delivering patient-controlled IV morphine or perineural ropivacaine 0.2%, either by continuous infusion or basal infusion with concomitant PCRA doses. Patients receiving IV PCA morphine experienced significantly more postoperative pain during movement and consumed more rescue medication than patients receiving continuous infusion or basal plus bolus ropivacaine ($P < .05$). Furthermore, patients in the IV PCA group experienced a higher incidence of adverse events, including nausea/vomiting, sleep disturbance, and dizziness. More mechanical problems (e.g., kinking, dislodgement, occlusion) were reported with IV PCA. Basal infusion with PCRA doses of ropivacaine was found to optimize patient recovery and pain relief, and was associated with the lowest consumption of analgesia and incidence of adverse events. Results obtained from this comparative trial support findings of a recent meta-analysis, which indicated that analgesia administered by continuous peripheral nerve block with local anesthetics provided significantly better postoperative analgesia ($P < .001$) and resulted in less

opioid-related adverse events compared with opioid analgesia.[63]

One of the main benefits of PCRA is that it can be used on an outpatient basis. However, in an unmonitored setting, there may be increased risk for potential complications (e.g., infection, leaking/disconnection of indwelling catheters, or potential injury to the insensate limb). Despite its invasiveness, PCRA displays the safety, efficacy, ability to titrate to comfort, and patient satisfaction required for a PCA system to be optimal, especially in orthopedic surgery patients.

Patient-Controlled Intranasal Analgesia (PCINA)

In its early stages of development, intranasal (IN) drug delivery was used predominantly to deliver locally acting agents to the nasal mucosa; however, in the past few years, increasing attention has been given to the administration of systemic agents via this route.[64] Intranasal opioids, either in the form of a dry powder or water or saline solution, are delivered using a syringe, nasal spray or dropper, or nebulized inhaler.[65] In addition to needle-free administration, IN opioid administration bypasses the hepatic first-pass effect, and due to the excellent perfusion of the nasal mucosa, displays rapid absorption and rise in plasma concentration.[66]

Fentanyl has been used in several PCINA devices due to its high lipid solubility, low molecular weight, and high potency, characteristics which make it well-suited for IN administration.[67] In the postoperative setting, fentanyl PCINA delivery using a Baxter PCA pump (Deerfield, Illinois) (modified with an adaptor for IN administration) was found to be superior to ward-provided therapy (pethidine, tramadol, metamizole, acetaminophen, codeine, and diclofenac, used either alone or in combination) in a pilot crossover study (N = 20).[68] Patients receiving PCINA had significantly lower pain scores than patients who received ward-provided therapy and patient satisfaction was greater with PCINA than with ward-provided therapy ($P < .0005$).[68]

A single-center, crossover pilot study compared the efficacy and safety of an IN, patient-controlled, spray bottle that did not require a pump to that of IV fentanyl administration for the treatment of acute pain following gynecologic surgery.[69] In that study, 50 μg of fentanyl was delivered per spray using the IN spray device or per infusion using fentanyl delivered via IV administration.[69] Pain intensity scores measured by the visual analog scale (VAS) were similar in the 2 groups, both at rest and after movement ($P = .78$); however, 17% of patients in the fentanyl IN group reported mild stinging in the nose following fentanyl administration, and 13% reported a bitter taste in the mouth. Forty-two percent of patients preferred IV analgesic administration, while 29% preferred IN administration.[69]

In comparisons of PCA modalities, fentanyl PCINA, delivered via an IN-adapted PCA pump, was found to be similar in efficacy to fentanyl IV PCA for postoperative pain relief.[70,71] In the first study,[70] the analgesic effect at 60 minutes following treatment initiation with fentanyl PCINA was comparable to that with fentanyl IV PCA. The 30-minute and 480-minute pain intensity scores were significantly reduced with both PCINA ($P < .001$) and IV PCA ($P < .001$) relative to baseline assessments. No significant between-group differences in pain intensity were noted, and no patients experienced problems with the PCINA device. In the second study,[71] PCINA and IV PCA were associated with comparable pain intensity scores, vital parameters, and side effects. Both treatments were associated with a similarly rapid onset of action, and provided high levels of patient satisfaction.

Another comparative study randomly assigned patients to receive diamorphine PCINA or diamorphine IV PCA.[72] Patients receiving PCINA reported higher VAS scores than those receiving IV PCA (median score 35.5 vs. 20.0, respectively; $P = .016$); however, more patients in the IV PCA group experienced vomiting compared with those in the PCINA group (0/24 vs. 6/24, respectively; $P = .022$).[72] It was speculated that technical difficulties associated with the PCINA device resulted in lower analgesic efficacy; specifically, in cases where the IN reservoir was not in the upright position, the desired dose of diamorphine may not have been delivered.[72] Reduced analgesia resulting from the drainage of opioid into the pharynx has also been suggested.[69] Results of a separate study evaluating patient acceptability of PCINA indicated that 79% of patients would want to use the modality again.[73]

The reported adverse effects of PCINA are mainly those that are related to the opioids rather than to IN administration.[74] However, there have been reported side effects related specifically to the IN or inhaled route, including a bitter, burning taste, stinging in the nose, coughing, and nasal pruritus.[65,69,75,76]

While evidence suggests that PCINA is efficacious, safe, noninvasive, and easy to administer, there have been only a limited number of randomized, placebo-controlled trials evaluating this route of analgesic administration. Although further research may address these problems, some authors have suggested that IN administration of opioids for postoperative pain relief is not likely to supersede

other techniques, but rather play a role in the management of acute pain in children and patients for whom IV access is difficult.[65] In addition, IN ketamine has been studied for the management of breakthrough pain in patients with chronic pain.[77] However, the use of IN ketamine for the management of postoperative pain has not been evaluated.

Fentanyl Iontophoretic Transdermal System (ITS)

The fentanyl ITS (IONSYS™, Ortho-McNeil, Inc., Raritan, NJ) is a needle-free, compact, self-contained preprogrammed fentanyl delivery system that does not require venous access for administration. Instead, it adheres to the patient's upper outer arm or chest via an adhesive backing, and through iontophoresis, uses a low-intensity electrical field to transfer fentanyl from a gel reservoir across intact skin. The system delivers 40 μg of fentanyl per on-demand dose, and it can deliver up to 6 doses per hour for up to 24 hours or 80 doses per system (whichever comes first), thereby allowing patients to titrate analgesia to comfort. Each dose is delivered over a 10-minute period, during which the system is unresponsive to additional medication requests.

The fentanyl ITS was shown to be superior to placebo for the management of acute postoperative pain in randomized, double-blind trials.[78,79] Adult patients who had undergone major abdominal, orthopedic, or thoracic surgery and were expected to have moderate-to-severe postoperative pain were included in both trials. Results from the first trial[78] showed that the fentanyl ITS was superior to placebo on all efficacy measures, including fewer withdrawals due to inadequate pain control ($P < .05$), lower last pain intensity score ($P = .047$), higher patient global assessment ($P = .047$), and higher investigator global assessment ($P = .007$). Results of efficacy endpoints from the second randomized, placebo-controlled trial[79] supported data from the previous study. Additional endpoints, in the form of patient questionnaires assessing satisfaction, ease of use, and convenience were included. The fentanyl ITS was superior to placebo on all of these measures; patients were very satisfied with the pain management provided, and considered the system convenient and easy to use.[79]

The fentanyl ITS has also demonstrated efficacy similar to a standard regimen of morphine IV PCA for the management of acute postoperative pain in a number of active-controlled clinical trials.[80-83] In the first trial,[80] therapeutic equivalence (defined as the 95% confidence interval of the difference in success rates falling within ± 10%) was demonstrated, with 73.7% of patients who received fentanyl ITS and 76.9% of patients who received morphine IV PCA rating their pain control a success (rating of "excellent" or "good" on the patient global assessment), at 24 hours (difference = −3.2%; 95% confidence interval, −9.9% to 3.5%; $P = .36$). Pain intensity ratings (measured on a VAS) also did not differ significantly between groups at any assessed time point.[80] Both groups had a similar incidence of common opioid-related adverse events, such as nausea, headache, vomiting, and pruritus.

No episodes of clinically relevant respiratory depression (defined as a respiratory rate <8 breaths/minute coupled with excessive sedation) were reported in patients using fentanyl ITS in any of the placebo- or active-controlled trials,[78-83] while 5 patients receiving morphine IV PCA in the active-controlled trials developed clinically relevant respiratory depression.[80-83] The most common treatment-related adverse events in patients receiving fentanyl ITS were skin application site reactions, the majority of which were mild to moderate in nature and resolved spontaneously without treatment.[78-83]

Evaluation of secondary outcome measures in 2 active-controlled trials has demonstrated that compared with morphine IV PCA, the fentanyl ITS is associated with a more favorable assessment of ease of use and ease of patient care from the perspectives of patients and the nurses that cared for them.[81,82] Upon completion of the studies, patients and nurses completed Ease-of-Care Questionnaires that contained an extensive list of subscale items scored on a 6-point Likert scale. In both studies, significantly higher percentages of patients and nurses in the fentanyl ITS group were responders (defined as patients and nurses who responded with 1 of the top 3 responses of the Likert scale on all items of a subscale) for Overall Ease-of-Care compared with those in the morphine IV PCA group.[81,82] The fentanyl ITS utilizes a noninvasive route of administration and does not require additional attachments that may hinder patient mobility. In fact, significantly higher percentages of patients and nurses in the fentanyl ITS group vs. the morphine IV PCA group were responders on the Movement subscale (measuring ease of mobility) in both studies.[81,82]

Fentanyl ITS has demonstrated an acceptable safety profile and efficacy superior to that of placebo and comparable to that of IV PCA.[78,84] Furthermore, the preprogrammed nature of fentanyl ITS eliminates the potential for medication errors due to inaccurate programming and possible "drug swaps." While the elimination of the programming step is certainly a positive feature of the fentanyl ITS, it also removes the possibility of using a basal

infusion in addition to the PCA therapy. Therefore, fentanyl ITS may not be appropriate for patients with a need for a basal infusion, such as those who are opioid-tolerant. Another potential limitation to fentanyl ITS is the fixed 40 μg dose, which cannot be adjusted to meet individual opioid requirements. However, pooled data from 3 active-controlled studies[84] (N = 1,941) comparing the efficacy of fentanyl ITS and morphine IV PCA demonstrated that similar rates of successful pain control were achieved with both modalities, regardless of age or body mass index. Another limitation of fentanyl ITS is that it may only be used for a maximum of 24 hours before it must be discarded and replaced with a new system, which has the potential to result in analgesic gaps if a patient is not administered a new system in a timely fashion, and may also result in unnecessary cost if a system is applied and not used within 24 hours. Also, while the compact, preprogrammed design of fentanyl ITS may afford increased patient mobility and ease of use, it also has the potential to be more easily concealed, stolen, and abused by hospital staff members and visitors compared with IV PCA or PCEA. Abuse of fentanyl patches, which are indicated for outpatient management of chronic pain, is well documented,[85,86] and special care may be necessary to prevent similar cases from occurring with fentanyl ITS. However, because fentanyl ITS is only approved for inpatient use, the potential for abuse is minimized compared with the potential for abuse with the fentanyl patch. Finally, there exists potential for detachment of the fentanyl ITS from the patient's skin, although evidence indicates that this is a low probability event.[87]

Other PCA Modalities

Other PCA modalities are also worthy of note, but were not highlighted in this review because they are either not intended for the management of postoperative pain, or because sufficient data about their efficacy, safety, or comparisons with other PCA modalities are not available. Oral transmucosal fentanyl,[88] the fentanyl buccal tablet,[89] and the fentanyl transdermal matrix patch applied with controlled heat-assisted drug delivery (CHADD),[90] are currently indicated or under development for patient-controlled treatment of breakthrough chronic cancer or non-malignant pain, but are not expected to play significant roles in managing postoperative pain. Patient-controlled transpulmonary fentanyl[91,92] and morphine[93] modalities have also been assessed for the management of postoperative pain. A recent report[94] of preliminary data from a phase IIb trial suggests that one fentanyl transpulmonary system (AeroLEF™; YM BioSciences Inc., Ontario, Canada) is superior to placebo for providing postoperative pain relief in opioid naïve patients following orthopedic surgery; however, sufficient data from the biomedical literature are lacking to adequately compare the usefulness of transpulmonary modalities to that of other postoperative PCA modalities. Future developments in these and other PCA modalities should be carefully considered to optimally address the current unmet needs of postoperative pain care.

Conclusions

IV PCA and PCEA have been safely and effectively used for postoperative pain management for several decades, but their use is associated with limitations that have led to the development of other patient-controlled modalities, including PCRA, PCINA, and fentanyl ITS (IONSYS™).

PCRA has demonstrated efficacy, safety, and patient satisfaction; however, PCRA is administered via an invasive route, requiring the use of an indwelling catheter. One of the main benefits of PCRA is the opportunity for outpatient use. Therefore, PCRA has the most potential for benefiting ambulatory orthopedic patients who have undergone same-day orthopedic surgery, as unmet analgesic needs have been identified in this patient population.

Several studies have demonstrated the safety and efficacy of PCINA. PCINA modalities are minimally invasive and are easy to use, and patient satisfaction was reported to be high; however, only a limited number of randomized, placebo-controlled trials have been performed thus far. PCINA has the potential to significantly enhance postoperative pain control because of the inherent simplicity and noninvasiveness of its administration. However, improvements in the delivery apparatus are required to provide optimal and reliable pain management for patients.

Fentanyl ITS is a preprogrammed, self-contained, drug delivery system that provides the benefits of IV PCA without the associated lines, tubing, and IV pole. Because of the technology required for the accurate, on-demand administration of analgesia across intact skin, the enhanced ease of use of fentanyl ITS is not derived from an inherent simplicity as is the case for PCINA, but rather an achieved simplicity founded in the application of a sophisticated, yet easy to use system. Fentanyl ITS has been demonstrated to be safe and effective for postoperative pain management in several large, randomized clinical trials, with efficacy equal to that of a standard regimen of morphine IV PCA.[80-83] Fur-

thermore, the system is noninvasive and convenient, and patients were highly satisfied with its use. Fentanyl ITS is approved in the United States by the Food and Drug Administration and in Europe by the European Medicines Agency for the treatment of acute postoperative pain in hospitalized adults.

An important issue to consider when evaluating the feasibility and overall value of PCA modalities is cost. Several studies have estimated the cost of an episode of IV PCA,[17,21,95-97] and one recent German study estimated the cost of an episode of PCEA.[98] However, it is difficult to compare cost data between sites and countries, and comprehensive studies that have assessed all the direct (e.g., equipment, consumables) and indirect (e.g., staff time, hospital overhead) costs associated with administering PCA are few and far between. As noted by Hudcova and colleagues,[99] one particular advantage of PCINA and transdermal PCA modalities (e.g., fentanyl ITS) compared with IV PCA may be reduced costs associated with staff labor and acquired staff expertise. The compact, simple design of both PCINA and fentanyl ITS may eliminate many of the complex steps necessary for administering modalities that require PCA pumps,[100] as well as many of the costly medication errors that are associated with mistakes in PCA pump programming.[10,25,26]

Patient-controlled or patient-activated analgesia systems offer distinct advantages over traditional intermittent dosing approaches. Self-titration generally leads to greater patient satisfaction, and with some technologies, enhanced analgesia. Pump technologies, while effective, may require considerable attention from health care providers, and in some cases, may be associated with programming or medication errors. New and emerging PCA technologies may address some of these issues.

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