Benefits of Extending the Duration of a Local Analgesic as Part of a Multimodal Regimen for Postsurgical Pain

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Introduction
Poorly managed pain in the postoperative period is common and can be associated with worsened outcomes, higher costs of care, reduced patient satisfaction, and an increased risk for developing chronic pain syndromes. Over the past 2 decades, multimodal and preemptive analgesia strategies have been developed in an effort to facilitate improved pain control for postsurgical patients. Among the various techniques and pharmacologic agents employed within these strategies are several classes of local anesthetics/analgesics, which can be quite effective in reducing postsurgical pain.

This review will provide a brief overview of postsurgical pain, discuss the concepts of multimodal analgesia and preemptive analgesia, and present the potential role of current and emerging local anesthetics in improving the control of postsurgical pain.

Epidemiology and Consequences of Postsurgical Pain
Acute pain is common after many types of surgeries. In a telephone survey of adults who had surgical procedures, Apfelbaum and colleagues reported that approximately 80% (n=250) of patients experienced acute postsurgical pain, and of these patients, 86% had moderate, severe, or extreme pain. The time course of postsurgical pain can be protracted. Lynch and colleagues assessed pain after elective noncardiac surgery through the use of questionnaires and a visual analog scale in 276 patients. They reported that the mean maximum pain score on postsurgical day 1 was 6.3 (moderate pain) and decreased only slightly to 5.6 by postsurgical day 3. Beauregard and colleagues assessed pain using questionnaires in 89 patients who underwent ambulatory surgery. They found that 40% of patients reported moderate to severe pain during the first 24 hours after discharge and that pain decreased over time but was severe enough to interfere with daily activities, even several days after surgery. Inadequate management of acute postsurgical pain often results in decreased mobilization, which can increase the probability of pneumonia and venous thromboembolic disease. The psychological effects of uncontrolled pain, including depression and anxiety, can also contribute to poor patient outcomes and decreased patient satisfaction. Furthermore, Perkins reported that uncontrolled postsurgical pain was the main predictor for development of chronic pain syndromes and that improved postsurgical analgesia reduced the incidence of this complication.

Postsurgical pain also is associated with decreased long-term function as well as increased resource utilization and health care costs. For example, Morrison and colleagues studied 411 patients undergoing surgical repair of a hip fracture and reported that patients with higher postsurgical pain scores had significantly longer hospital length of stay (LOS), were significantly less likely to be ambulating by postsurgical day 3, took significantly longer to ambulate further than a bedside chair, and had significantly lower locomotion scores at 6 months.

Coley and colleagues reported that postsurgical pain was the most frequent reason for hospital readmission after discharge. Strategies to Improve Postsurgical Pain Management
Opioid monotherapy remains a widely used mode of postsurgical analgesia. Patient-controlled analgesia (PCA) pumps have improved the delivery of opioids in the inpatient setting; however, they can be subject to programming errors, device malfunctions, and patient tampering. Although this strategy can be effective in some cases, opioids have various adverse effects (AEs) that curtail their practical efficacy as well as expose patients to dangerous complications. For example, central nervous system effects associated with opioids, such as sedation and respiratory depression, are particularly dangerous. Other AEs are common even at low doses, such as nausea, vomiting, and ileus, which can result in significant discomfort and longer hospital LOS. Still other opioid-related AEs, such as urinary retention, can necessitate further procedures or treatments (such as urinary catheters) and their associated discomforts and costs. In one study of hospitalized patients, urinary retention was associated with an increase in cost of $777 per patient, correlating with a percentage increase in cost of 14.5% (Table). Over a 10-year period of surveillance, more than 60,000 patients were observed who received opioids following surgery. More than 1,000 adverse drug events (ADEs) were observed in this cohort. It was determined that 59% of these ADEs involved an opioid, accounting for an adjusted increase in LOS of 0.53 days.

Other drug classes, such as nonsteroidal anti-inflammatory drugs (NSAIDs) administered orally or intravenously, have been shown to reduce overall use of narcotic post-surgery, thereby reducing the frequency of AEs related to bowel function and narcotic use. Recent initiatives to improve management of postsurgical pain cite the potential effectiveness of multimodal analgesia and preemptive analgesia. Multimodal analgesia is defined as the simultaneous use of different classes or modes of analgesics that modulate different pathways and receptors in order to provide superior pain control (Figure). Multimodal analgesia provides several benefits to postsurgical patients. First, use of agents with different analgesic mechanisms can result in synergistic effects and thereby produce greater efficacy. Second, the synergism between these agents may allow for the use of lower doses of each respective agent, thereby limiting dose-related AEs, particularly when these regimens allow lower doses of opioids. These actions, in turn, may facilitate earlier mobilization and rehabilitation after surgery, earlier transition to the outpatient setting, and decreased costs of care.

Local Anesthetics as a Component of Multimodal Analgesia
Local anesthetics, which impede the transmission of noxious signals by blocking sodium channels in neurons, are used in a variety of ways for postsurgical pain control. Strategies include the use of local anesthetics in epidural anesthesia as well as for various types of peripheral nerve blocks, as well as via continuous infusion using either elastomeric or electronic pumps. However, continuous infusion of local anesthetics via indwelling catheters can be associated with complications (eg, bleeding, accidental dislodgement or migration, infection, paresthesias, dysesthesias, pain not related to surgery) and is not particularly suited to use in the ambulatory setting.

Another method of using local anesthetics is via infiltration of the wound during the final stages of the surgical procedure, which can be used alone or in combination with other analgesic regimens. Because the mode of delivery does not require an indwelling catheter, it may be better suited to facilitating earlier discharge from the hospital or for effective pain control following surgical procedures. The use of local anesthetics as a component of multimodal analgesics instead of opioids obviates the chance of opioid-induced AEs and reduces nursing workload, while the analgesic action of the drug can still control resting pain and pain on motion, thereby fostering patient mobility.

Almost all local anesthetics can be effectively used for wound infiltration, but local anesthetics with longer duration of action are preferred. The high lipid solubility of bupivacaine lends itself to the treatment of postsurgical pain. In particular, bupivacaine offers a rapid onset and provides one of the longer durations of activity of the commonly used extended duration local anesthetics.

New formulations of bupivacaine that can extend its duration of action are being developed. A multivesicular liposomal formulation, DepoFoam® bupivacaine, can extend the duration of action from 6 to 9 hours to up to 72 hours and is therefore better suited to the natural time course of postsurgical pain. Studies of this agent in a variety of surgical contexts, including hernia, hemorrhoidectomy, breast augmentation, bunectomy, and total knee arthroplasty, demonstrated a statistically
significant decrease in pain and/or opioid requirements for up to 3 days.\textsuperscript{30,37} For instance, DepoFoam bupivacaine was studied in 2 pivotal Phase III randomized, placebo-controlled trials in patients undergoing hemiorthoracotomy and bunionectomy. In the trial of 189 patients undergoing Milligan-Morgan hemiorthoracotomy, a significant decrease in total opioid use was noted in the DepoFoam bupivacaine group. In addition, the time to first opioid use following surgery was significantly extended compared with the placebo group (14.3 vs 1.1 hours, respectively). Similar results were demonstrated in the bunionectomy study. Reducing opioid use after surgery may be clinically beneficial in the management of postsurgical pain.\textsuperscript{98}

In addition to improving patient outcomes and satisfaction, improved pain management has the potential to lead to early ambulation and reduced health care costs by decreasing hospital LOS, as well as minimizing the need for patient admission/readmission. Other multimodal strategies regarding the use of local anesthetics/analgesics as part of the multimodal armamentarium usually include continuous infusion and may be associated with complications.\textsuperscript{30,32} Some of these issues could be addressed by a local analgesic with an extended duration.

**Conclusion**

The use of a multimodal regimen can improve postoperative pain control; infiltration with a long-acting local anesthetic/analgesic has the potential to become a foundation of multimodal pain control. New formulations of local anesthetics/analgesics with an extended duration of action are under development and may better match the time course of postsurgical pain. Thus, these new agents may help reduce health care expenditures through reduction in hospital LOS, facilitation of pain control following surgery, avoidance of opioid-related costs and AEs, and improved patient satisfaction.

**References**


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