Evolving Role of Local Anesthetics in Managing Postsurgical Analgesia

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ABSTRACT

Purpose: Opioid analgesics, the cornerstone of effective postsurgical pain management, may be associated with risk of opioid-related adverse drug events (ADEs) that may complicate the postsurgical experience. Perioperative multimodal analgesic regimens have the potential to improve postsurgical pain control and may permit use of lower analgesic doses and reduce the incidence of opioid-related ADEs. Utility of traditional local anesthetic formulations to provide analgesia over the entire postsurgical period is limited by their short duration of action. Liposome bupivacaine, a liposomal formulation of bupivacaine indicated for single-dose administration into the surgical site to produce postsurgical analgesia, was evaluated in multiple surgical models as part of multimodal analgesic regimens and was found in clinical trials to provide postsurgical analgesia for up to 72 hours. Here, we provide an overview of the available multimodal analgesic options and recent recommendations for optimal postsurgical pain management.

Methods: A review of the literature was conducted, and results from recent clinical trials are included.

Findings: The use of a multimodal analgesic regimen, including liposome bupivacaine, can extend the time to first postsurgical opioid use, may reduce postsurgical opioid consumption, and reduce hospital length of stay and costs compared with an opioid-only analgesic regimen.

Implications: Use of multimodal analgesic regimens is a practical way to achieve good postsurgical analgesia while minimizing reliance on opioids and associated adverse events. Taken as a whole, evidence from the clinical studies of liposome bupivacaine suggests this local anesthetic formulation may be a useful component of multimodal analgesic regimens for managing postsurgical pain in select patients, with the potential to reduce opioid use and opioid-related ADEs in the postsurgical setting. As with bupivacaine, appropriate use of liposome bupivacaine to optimize clinical effects, economic implications, and patient tolerability will depend on appropriate patient selection, practitioner training, and institutional protocols. As a component of a multimodal analgesic regimen, liposome bupivacaine represents a new approach to extending the duration of postsurgical analgesia. Further studies across a range of surgical settings should help clarify the most appropriate roles for this prolonged-release formulation of bupivacaine. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: bupivacaine, local anesthetics, multimodal analgesia, opioid analgesics, postoperative pain.

INTRODUCTION

Pain management is a prominent issue for health care practitioners and patients. It is estimated that >70 million surgical procedures are performed annually in the United States, and most surgical patients experience moderate-to-severe pain after surgery.[1,2] Over the past few decades, the focus has increased on improving the quality of pain management (including postsurgical pain), reflected in standards and/or guidelines established by a range of governmental and health care organizations.

Clinical recommendations and benchmarks for managing postoperative pain were published by the Office of the Forum for Quality and Effectiveness in Health Care of the Agency for Healthcare Research and Quality (AHRQ; formerly the Agency for Health Care Policy and Research) in 1992 to provide a resource to help clinicians better recognize, assess,

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and manage postoperative pain.[3] Specific recommendations to facilitate the efficacy and safety profile of acute pain management in the perioperative setting were originally published by the American Society of Anesthesiologists in 1995[4] and updated in 2004 and 2012.[5,6] Institutional responsibility for ensuring adequate pain management has become a key focus of several organizations, including the AHRQ.[3] In 2000, the Veterans Health Administration formally designated pain as "the fifth vital sign," and published guidelines for pain management.[7] The Joint Commission (formerly known as the Joint Commission on Accreditation of Healthcare Organizations) established standards for pain management in 2001, clarifying that pain management was an "institutional responsibility."[8,9] Jointly developed by the Centers for Medicare and Medicaid Services and the AHRQ, the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey was implemented in 2006 to measure patients' perceptions of their hospital experiences (including 2 questions focused specifically on pain management).[10] With respect to pain management, the HCAHPS survey assesses the effectiveness of patient education provided by health care practitioners (eg, expectations, management plan, and possible medication side effects) and how well hospital staffs respond to patient needs. Since 2007, HCAHPS survey reporting was required for institutions to receive annual payment updates; the Affordable Care Act of 2010 mandates that HCAHPS survey data be included in the calculation of value-based incentives, beginning October 2012.[10]

However, despite these concerted efforts to improve pain management and the growing armamentarium of analgesic compounds and technologies that govern their use, it appears little improvement was made during the past 20 years, particularly in the area of postsurgical pain management.[11] In 1995, Warfield and Kahn[12] reported results from a survey of US adults (N = 500) of whom 27% had undergone surgery within the previous 5 years. Of the patients who experienced postsurgical pain, 80% reported pain of moderate, severe, or extreme severity. Moreover, only 53% received counseling about postsurgical pain. The investigators concluded that the AHRQ pain management guidelines released during the year before the survey had little influence on actual pain management practices.[12]

About 10 years later, Apfelbaum et al[2] conducted a similarly designed survey in a random sample of 250 adults who had recently undergone surgical procedures in the United States. Approximately 80% of respondents experienced acute pain after surgery. Of them, 86% had moderate, severe, or extreme pain. Almost 25% of the 205 patients who received pain medications experienced adverse effects; however, almost 90% of them were satisfied or very satisfied with their pain medications.[2]

More recently, Gan et al[13] reported similar results in a survey of 300 surgical patients. In this group, 85% of patients reported they had experienced acute postsurgical pain. Pain intensity was moderate, severe, or extreme in 75% of these patients, and ~80% reported an adverse drug event (ADE), most of which were consistent with opioid use.[13]

ANALGESIC MECHANISMS OF ACTION

Frequently used analgesics that have reported efficacy in the management of postsurgical pain include acetaminophen, gabapentinoids, local anesthetics, NSAIDs, opioids, and, to a lesser extent, the N-methyl-D-aspartate receptor antagonist ketamine and alpha-2-adrenergic agonists.[6,14–16] **Figure 1** depicts selected analgesic classes and the areas they target within the central nervous system (CNS) and periphery. The mechanism underlying acetaminophen-induced analgesia remains unclear, although its analgesic effects are thought to be from activation of descending serotonergic pathways and inhibition of prostaglandin synthesis in the CNS.[16–18] Alpha-2 agonists act at the level of the alpha-2 receptor, primarily in the CNS, and may be most useful administered as an intrathecal injection or epidural infusion.[11,16] The pharmacologic actions of gabapentinoids are thought to be related to their affinity for the alpha-2 delta-1 subunits of voltage-gated sodium channels in CNS tissues, which results in reduction in the synaptic release of excitatory neurotransmitters and neuromodulators.[19] Local anesthetics block the voltage-gated sodium channels, thereby blocking nerve conduction; they may act at the site of injury (affecting nociceptive-free nerve endings and, possibly, motor nerve fibers), on peripheral nerves (where they affect nociceptive and motor nerve transmission in a major nerve or nerve plexus), or at the spinal level.[11,16,20] Opioids act primarily within the CNS, where they target specific opioid receptors involved in transmission of pain signals, although they may exert some peripheral