10.5005/jp-journals-10017-1048

REVIEW ARTICLE

Proper Postsurgical Pain Management in Orthopaedics: Reviewing the Efficacy of Wound Infiltration with Liposomal Bupivacaine (EXPAREL)

[1]Vani Sabesan MD, [2]Timothy R Jelsema MS, [3]Daniel J Lombardo MD

ABSTRACT

Adequate postoperative pain management after an orthopaedic procedure is critical for patient well-being, acceptable clinical outcomes and patient satisfaction. Current literature suggests over 80% of surgical patients' state they have moderate to severe pain within 24 hours postoperatively. The standard in pain management for more than 40 years has been opioids, medications known for their many adverse effects and limited efficacy. Recently, a multimodal approach to pain control has been sought after for optimal postoperative pain management. This approach utilizes multiple methods of pain management, such as nerve blocks, wound infiltration with local anesthetics and oral analgesics, to concomitantly reduce postoperative pain. Liposomal bupivacaine, EXPAREL, has been shown to reduce pain for as long as 96 hours postoperatively in select studies. These studies have included both hard and soft-tissue procedures. The goal of this review is to examine the literature on EXPAREL and provide a comprehensive presentation for orthopaedic surgeons to apply to their practices.

Keywords: EXPAREL, Bupivacaine, Liposomal, Orthopaedics, Postoperative management, Pain.

Sabesan V, Jelsema TR, Lombardo DJ. Proper Postsurgical Pain Management in Orthopaedics: Reviewing the Efficacy of Wound Infiltration with Liposomal Bupivacaine (EXPAREL). The Duke Orthop J 2015;5(1):6-9.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

For surgical patients, rehabilitation and patient outcomes are optimized when postoperative pain is effectively managed.[1] Studies cite 77 to 80% of surgical patients experience postoperative pain, and 21 to 86% of those patients state the pain is moderate to extreme in nature.[2,3] In orthopaedics, postoperative pain control is critical for successful outcomes. Patients with postsurgical pain are less likely to ambulate by postoperative days 3 and have decreased range of motion, relative to their pain-free counterparts, 6 months after their procedure.[3,4] Furthermore, patients experiencing postoperative pain have reduced sleep, motivation, daily functioning, and personal affect than those with well-managed pain, making postoperative pain management critical for good outcomes, both short-term and long-term.[5]

Opioid monotherapy has been the standard of care for postoperative pain management for over 40 years.[1] Unfortunately, opioids have been repeatedly shown to be inferior to multimodal care and have shown a proclivity for drug-related adverse events—events that affect more than just a patient's health. Studies cite that upward of 31% of patients on opioids experience constipation or vomiting, 30% experience excessive sedation and 2.8% experience respiratory suppression. Furthermore, patients experiencing an opioid related event can expect a 55% longer stay, a 47% increase in cost, a 36% chance of being readmitted within 30 days, and a 3.4 times increased risk of inpatient death.[1,2,5-8] These detrimental outcomes have led to a paradigm shift toward multimodal care, reviving the focus on pain as the 'fifth vital sign' in an attempt to curtail the effect of pain on patient outcomes.[7] An initial shift to multimodal care occurred in the 1990s to relieve the dependence on opioid analgesics. The idea of multimodal pain control has experienced a resurgence in light of studies that demonstrate a correlation between reduced cost and length of stay, increased time to first opioids, and reduced total opioids used among multimodal care patients.[9]

Multimodal Management

Orthopaedic procedures are associated with substantial pain, but are some of the most cost-effective procedures modern surgery can offer.[10] Improvement after these procedures is frequently limited by the patient's ability to ambulate and rehabilitate themselves soon after their respective procedures. To this extent, multimodal approaches have begun supplanting opioids as the preferred method of postoperative pain management due to excessive somnolence and untoward effects associated with opioids.

[1]Associate Professor, [2]Medical Student, [3]Resident

[1-3]Department of Orthopaedic Surgery, Wayne State University School of Medicine, Suite, Dearborn MI, USA

Corresponding Author: Vani Sabesan, Department of Orthopaedic Surgery, 18100 Oakwood Blvd, Suite 305, Dearborn MI 48124, USA, Phone: 313-375-7218, e-mail: sabes001@gmail.com

Multimodal approaches inhibit multiple pain processing pathways simultaneously. This allows for lower dosages of each medication to be used, including opioids.[8] Mechanisms, such as peripheral nerve blocks, neuraxial analgesia, NSAIDs, and local anesthetics, have all been used to provide synergistic pain relief.[1] Local anesthetics have shown great promise in soft-tissue surgical procedures, and have been adjusted to provide longer acting pain relief immediately following surgery when infiltrated into the surgical site.[11] Also, unlike opioids or nerve blockade, local anesthetics do not cause sedation or motor blockade following surgery, impairments that leave the patient at an increased risk for falls.[12]

Liposomal Bupivacaine (EXPAREL)

Liposomal bupivacaine (LB), or EXPAREL (Pacira Pharmaceuticals Inc, Parsippany, NJ, USA), is a slow release formulation of the local anesthetic bupivacaine HCl. LB has a half-life of 24 to 36 hours, which is 12 to 18 times longer than that of Bupivacaine HCl. Also, liposomal bupivacaine has a bimodal peak blood concentration because it is comprised of 3% bupivacaine HCl and 97% liposomal formulation.[3,5,6,13] Liposomal bupivacaine is comprised of bupivacaine placed into a spherical, honeycombed, lipid-based particle that ranges in size from 10 to 30 μm. The lipid sphere is a proprietary technology called 'DepoFoam', which is made of endogenous and biodegradable components, such as fatty acids, cholesterol, triglycerides and other lipids.[3,6,13] Once introduced into the surgical site, these particles degrade and slowly release the encapsulated Bupivacaine.[6] The liposome is resistant to degradation from antibiotics, steroids, morphine and epinephrine, increasing its clinical versatility and utility, while reducing the risk for drug-drug interactions or toxicity.[14] The concentration of bupivacaine inside the liposomes is 1.3% (13.3 mg/ml).[8]

Liposomal bupivacaine is flooded or injected into the surgical site by a surgeon prior to closure of the surgical wound, with the frequent aspiration to avoid intravascular injection.[8] Toxicity of LB is similar to that of other amide based local anesthetics, with the main concern being cardiotoxicity related to prolongation of the QTc interval. In studies assessing LB toxicity, QTc was not lengthened even after exceeding the maximum recommended dose. Also, safety studies indicated there was no increased risk for T-wave or PR-interval changes, and no increased risk of Torsades de Pointes.[2,14,15] Although side-effects as a whole were rare, the most commonly reported problems were transient tachycardia or bradycardia, nausea, vomiting and constipation. Pooled data of the 10 primary studies on the safety and efficacy of LB indicated that incidence of treatment-induced nausea for LB in concentrations under 266 mg, over 266 mg and for bupivacaine HCl, were 3.3, 2.2 and 4.3% respectively.[14]

Liposomal bupivacaine is primarily metabolized in the liver via conjugation with glucuronic acid and is subsequently excreted by the kidneys.[6] Roughly, 6% is excreted in the urine unchanged.[6,8] Although LB is contraindicated in patients younger than 18 years of age, those with severe liver or renal failure and, those with liver failure, it was not shown to have significant issues with metabolism in those populations.[6,13] With regards to wound healing and chondrolysis, two major concerns for local anesthetic infiltration, liposomal bupivacaine was not shown to increase healing time when assessing factors, such as erythema, discharge and drainage, induration and edema.[1,14,16] Liposomal bupivacaine was approved in October of 2011 as a single use injection/infiltration medication for management of acute pain, and is available in 20 ml solutions containing 266 mg of active drug.[1,3,8,17]

Liposomal Bupivacaine in Orthopaedics

The general and orthopaedic surgery literature extensively report on short acting local anesthetics. Unfortunately, the research into long-acting local anesthetics, such as LB, is limited, particularly in orthopaedic procedures. Even studies of short-acting anesthetics have typically examined pain management after soft-tissue procedures like breast augmentation, hernia repair, ileostomy reversal, and hemorrhoidectomies, with only a few focusing on hard-tissue procedures like total knee arthroplasty (TKA), total hip arthroplasty (THA), and bunionectomy.[4,5,9,14,17,18] While there is a general consensus that short-acting local anesthetics provide superior outcomes to opioids, many studies are not adequately blinded and many introduce additional variables by utilizing different systemic analgesics between the test and control groups.[4] These studies were often placebo-controlled trials that utilized drugs with 2 to 6 hours half-lives, such as ropivacaine, bupivacaine and levobupivacaine.[4]

Only two clinical trials have assessed the utility of LB in orthopaedic procedures. These two studies both examine the efficacy in postsurgical pain management of LB in patients undergoing TKA.[19] Unfortunately, the results were not as conclusive as those seen in soft-tissue studies of LB, where LB was seen to provide superior analgesia postoperatively.[17,18,20]

Bramlett et al performed a randomized, multicenter, doubled-blinded, dose-ranging study of LB in 138 patients undergoing TKA.[19] The study compared adverse effects (AEs) of LB with bupivacaine HCl at varied doses. Their results showed that the two drugs had similar AEs, but

did not elucidate the efficacy of one drug over the other in regards to postoperative pain management.

Bagsby et al performed a retrospective cohort study on all TKA procedures performed at one surgical center, by two specialists, from January-September 2013. Injections comprised of LB or a combination of ropivicaine, morphine, and epinephrine were administered at the end of each arthroplasty. Out of 150 total patients, 85 received the ropivacaine formulation, while 65 received LB. Pain was subjectively assessed via a 10-point visual analog scale (VAS) every 2 hours. Postoperative pain management from after the first 24 hours until time of discharge was the only pain that was noted to be significantly reduced between the two groups, with those given LB reporting higher scores ($p = 0.04$).[21]

DISCUSSION

Local anesthetics have been repeatedly shown to play an integral role in multimodal pain management in the postoperative setting, particularly when flooded or injected into the surgical wound prior to surgical closure. Recent studies indicate that LB, with its delayed release liposome core, can reduce pain for upward of 96 hours immediately following surgery in soft-tissue procedures. It also reduces the necessity of opioids for managing pain, allowing NSAIDs and other analgesics that have fewer AEs to be employed for breakthrough pain. Furthermore, studies have shown that LB does not impede wound healing, is associated with higher patient satisfaction regarding pain management, decreased length of stay in the hospital, and decreased overall hospitalization cost to the patient.[19, 22, 23] All of these variables have been shown to reduce morbidity and mortality in the hospitalized patient through reduction of risk factors, such as falls, infections and respiratory depression.

Unfortunately, literature on the use of LB in orthopaedic procedures is very limited; only being documented in two studies of TKA. These two studies have shown conflicting results for LB in adequately managing postsurgical pain after orthopaedic procedures. Since, orthopaedic procedures are some of the most cost-effective procedures in modern surgery, and because LB has shown such promise after soft-tissue procedures, it is important to understand the true effects of LB in these procedures. In order to clearly delineate the efficacy and utility of LB, additional blinded, well-controlled clinical trials are needed to provide generalizable results regarding the use of LB in orthopaedic procedures.

REFERENCES

1. Baratta JL, Gandhi K, Viscusi ER. Perioperative pain management for total knee arthroplasty. J Surgical Orthopaed Advances 2014;23(1):22-36.
2. Candiotti K, Haas E. Addressing current challenges in managing postsurgical pain with EXPAREL, a new Depo Foam formulation of bupivacaine. Anesthesiolo News 2012; 10(3):e1-9.
3. Portillo J, Kamar N, Melibary S, et al. Safety of liposome extended-release bupivacaine for postoperative pain control. Frontiers in Pharmacol 2014;5:90.
4. Andersen LO, Kehlet H. Analgesic efficacy of local infiltration analgesia in hip and knee arthroplasty: a systematic review. British J Anaesth 2014;113(3):360-374.
5. Barrington JW, Halaszynski TM, Sinatra RS, et al. Perioperative pain management in hip and knee replacement surgery. Am J Orthoped (Belle Mead, NJ). 2014;43(4 Suppl): S1-S16.
6. Massaro F. Liposomal bupivacaine: a long-acting local anesthetic for postsurgical analgesia. Formulary J 2012; 47(6):212-216.
7. Oderda GM, Gan TJ, Johnson BH, et al. Effect of opioid-related adverse events on outcomes in selected surgical patients. J Pain and Palliative Care Pharmacotherapy 2013;27(1):62-70.
8. Saraghi M, Hersh EV. Three newly approved analgesics: an update. Anesthesia Progress 2013;60(4):178-187.
9. Vogel JD. Liposome bupivacaine (EXPAREL(R)) for extended pain relief in patients undergoing ileostomy reversal at a single institution with a fast-track discharge protocol: an IMPROVE Phase IV health economics trial. J Pain Res 2013;6:605-610.
10. Busch CA, Whitehouse MR, Shore BJ, et al. The efficacy of periarticular multimodal drug infiltration in total hip arthroplasty. Clin Orthopaed Related Res 2010;468(8): 2152-2159.
11. Lunn TH, Husted H, Solgaard S, et al. Intraoperative local infiltration analgesia for early analgesia after total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. Regional Anesth Pain Med 2011;36(5): 424-429.
12. Andersen KV, Pfeiffer-Jensen M, Haraldsted V, et al. Reduced hospital stay and narcotic consumption, and improved mobilization with local and intraarticular infiltration after hip arthroplasty: a randomized clinical trial of an intraarticular technique vs epidural infusion in 80 patients. Acta Orthopaed 2007;78(2):180-186.
13. Lonner J. Role of liposomal bupivacaine in pain management after total joint arthroplasty. J Surg Orthopaed Advances 2014;23(1):37-41.
14. Viscusi ER, Sinatra R, Onel E, et al. The safety of liposome bupivacaine, a novel local analgesic formulation. Clin J Pain 2014;30(2):102-110.
15. Naseem A, Harada T, Wang D, et al. Bupivacaine extended release liposome injection does not prolong QTc interval in a thorough QT/QTc study in healthy volunteers. J Clin Pharmacol 2012;52(9):1441-1447.
16. Baxter R, Bramlett K, Onel E, et al. Impact of local administration of liposome bupivacaine for postsurgical analgesia on wound healing: a review of data from ten prospective, controlled clinical studies. Clinical Therapeut 2013; 35(3):312-320.e315.
17. Feierman D, Kronefeld M, Gupta P, et al. Liposomal bupivacaine infiltration into the tranversus abdominis plane for postsurgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients. J Pain Res 2014;7:477-482.

18. Gorfine SR, Onel E, Patou G, et al. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2011;54(12):1552-1559.
19. Bramlett K, Onel E, Viscusi ER, et al. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. The Knee 2012;19(5):530-536.
20. Minkowitz HS, Onel E, Patronella CK, et al. A 2-year observational study assessing the safety of DepoFoam bupivacaine after augmentation mammaplasty. Aesthetic surgery journal. Am Soc Aesthetic Plastic Surg 2012;32(2): 186-193.
21. Bagsby DT, Ireland PH, Meneghini RM. Liposomal bupivacaine versus traditional periarticular injection for pain control after total knee arthroplasty. J Arthroplasty 2014; 29(8):1687-1690.
22. Smoot JD, Bergese SD, Onel E, et al. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammaplasty: a randomized, double-blind, active-control study. Aesthetic Surg Journal. The Am Soc Aesthetic Plastic Surg 2012;32(1):69-76.
23. Langford R, Chappell G, Karrasch J. A single administration of DepoBupivicaine intraoperatively results in prolonged detectable plasma bupivacaine and analgesia in patients undergoing inguinal hernia repair. Annual Postgraduate Assembly in Anesthesiology of the New York State Society of Anesthesiologists. New York, NY; 2008.