

Review Article

Liposomal Bupivacaine in Managing Postoperative Pain Following Shoulder Surgery

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To optimize postoperative analgesia following shoulder surgery, current literature recommends multimodal approaches, including the use of regional liposomal bupivacaine (LB), a long-acting local anesthetic. The liposomal formulation of bupivacaine affords it a longer duration of action without a substantial peak plasma concentration; this combined with 3% free bupivacaine provides patients with substantial, prolonged postoperative analgesia following shoulder surgery. The use of LB as part of a multimodal approach to postoperative pain results in diminished use of

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Dr. Sabesan is passionate about research and leadership in her Orthopaedic community. She has published over 85 articles in the peer reviewed literature and has served on a number of regional, national, and international committees and boards, including the Florida Orthopaedic Society Board and program chair, American Shoulder and Elbow Society Research and Advocacy committees, AAOS Shoulder and Elbow Committee, International Society for Technology in Arthroplasty Board, Michigan Orthopedic Society Board, Mid America Orthopaedic Society, and American Orthopedic Association (AOA) Emerging Leader's program.

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opioids, reduced pain, and decreased length of hospitalization. Current literature supports these effects following a wide variety of shoulder procedures; however, some studies describe no benefit and list drawbacks including higher costs when electing to use LB instead of comparable, more affordable treatment modalities. In the interest of reducing the number of opioid prescriptions following orthopedic procedures, it is imperative to continue investigating the efficacy of LB as an opioid-sparing pain reducer. Recent literature suggests certain patient populations may be less suitable for implementing this treatment modality; namely those with a history of opioid use, prior surgeries, substantial systemic illness, and existing cardiopulmonary compromise. Patient demographics may be an additional consideration when determining the potential utility of LB to optimize analgesia after shoulder surgery.

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1. INTRODUCTION

Postoperative pain following shoulder surgery is a chief concern of patients when they undergo the decision-making process on whether to proceed with their operation (Yoon et al. 2012). Orthopedic procedures are considered some of the most painful procedures to endure in the first 48 hours following surgery (Gramke et al. 2007). In a prospective trial examining pain intensity on the fourth day postoperatively, Vrancken et al (Vrancken et al. 2018) identified procedures involving the shoulder joint to be associated with some of the highest levels of pain across all surgical specialties. Thus, postoperative pain management is an important consideration for surgeons performing shoulder operations.

Currently, a multimodal approach to postoperative pain management is an evolving practice following shoulder surgery (McLaughlin et al. 2018; M. S. Patel, Abboud, and Sethi 2020). Compared to the previously accepted standard of opioid prescriptions, a multimodal opioid-sparing approach to postoperative shoulder pain provides similar pain control and patient satisfaction with diminished opioid consumption (McLaughlin et al. 2018; Jildeh et al. 2021; Gazendam et al. 2022). Nerve blocks, nerve block adjuncts, subacromial injections, and non-opioid medications such as gabapentinoids and COX-II inhibitors serve as viable alternatives when constructing a postoperative pain management plan following shoulder surgery (Hurley et al. 2021; Cohn et al. 2021). Opioid-sparing postoperative pain management protocols have been shown to significantly reduce opioid consumption with reduced adverse effects and comparable levels of pain to those experienced by patients treated with opioid-based pain management therapies following shoulder procedures (Gazendam et al. 2022).

Interscalene brachial plexus blocks (ISB) are a common form of postoperative analgesia following procedures of the shoulder joint (White et al. 2022; Hussain et al. 2017). ISB's

are associated with a significant adverse effect known colloquially as “rebound pain” in which patients experience a spike in postoperative pain following the wearing off their interscalene block (Uppal et al. 2023; Lavand’homme 2018; Abdallah et al. 2015). Recently, liposomal bupivacaine (LB) injections have emerged as a viable supplement to interscalene blocks to increase the tolerability of pain, lower patient’s pain scores, and reduce opioid consumption in patients following shoulder operations (Lee et al. 2023). The utility of LB lies in its long-acting mechanism which has been shown to provide comparable pain relief with a similar frequency of adverse effects to non-liposomal local anesthetic agents in postoperative analgesia following shoulder surgery (Kolade et al. 2019). While injectable periarticular LB has shown promising outcomes when used as a singular agent, further investigations studies are necessary to fully establish its superiority compared to an ISB in controlling post-operative pain following shoulder arthroplasty (A et al. 2017). Interscalene blocks are associated with significant adverse effects such as Horner syndrome and diaphragmatic paresis secondary to phrenic nerve palsy in addition to pneumothorax and other respiratory or neurologic conditions (Hussain et al. 2017; Abdallah et al. 2015; Stasiowski et al. 2018; Marhofer et al. 2015; Bergmann et al. 2016; Bilbao Ares et al. 2013). Thus, the utility in using LB alongside an interscalene block following shoulder procedures lies in its potential to avoid the adverse effects associated with ISB’s while also reducing the “rebound effect” associated with ISB’s shorter duration of action.

2. MECHANISM OF ACTION OF LIPOSOMAL BUPIVACAINE

Liposomes are a type of microscopic structure composed of a hydrophobic phospholipid bilayer surrounding a hydrophilic aqueous center. This aquatic core can be filled

with different pharmaceuticals, including antibiotics, antifungals, chemotherapy agents, and local anesthetics (Liu, Chen, and Zhang 2022). Liposomes do not generate an immune response and have no intrinsic pharmacological behavior, positioning them as prime candidates for extended-release drug delivery systems (Pande 2023). Furthermore, liposomes increase drug biodistribution in their target tissues, thus overcoming barriers to cellular uptake (Guimarães, Cavaco-Paulo, and Nogueira 2021). Liposomes exist in three forms: unilamellar, multilamellar, and multivesicular. Unilamellar liposomes contain only one lipid bilayer surrounding the core; while multilamellar liposomes, as the name implies, consist of multiple concentric lipid layers encasing the aqueous center. Multivesicular liposomes (MVL) have multiple lipid layers like their multilamellar counterparts; however, these layers are nonconcentric, affording these formulations the advantages of increased stability and prolonged duration of drug delivery (Chahar and Cummings 2012). This makes MVL the formulation of choice for Exparel (Pacira Pharmaceuticals), the only LB product currently FDA-approved for use (Yu et al. 2023).

MVL containing a suspension of bupivacaine at a concentration of 13.3 mg/ml is packaged in 20 ml vials, resulting in a total bupivacaine load of 266 mg, delivered in a time-released fashion. Additionally of note, 3% of the total bupivacaine volume is in the form of free bupivacaine, which has profound implications on the pharmacokinetics of the product. Metabolic heat production causes the phospholipid layer encasing the active agent to degrade, resulting in a gradual release of the product, generally seen over a 72-hour timeframe. Bupivacaine plasma concentrations show a bimodal peak distribution, with the initial peak occurring shortly after administration, approximately within 2 hours, because of the rapid uptake of the 3% unencapsulated product. The second peak occurs between 12 and 36 hours, due to the delayed release of the liposomal-encased component (Hu et al. 2013). This contrasts with free bupivacaine, which shows a peak plasma concentration within 60 minutes of administration (Mazoit, Denson, and Samii 1988). Following release and uptake, bupivacaine is metabolized by the liver and excreted renally.

3. OPIOID OVERUSE IN SHOULDER SURGERY—AN ONGOING EPIDEMIC

The use of prescription opioids has increased significantly over the last three decades, and orthopedic surgeons are among the most common prescribers (Control CfD 2023a; Acuña et al. 2021; Guy and Zhang 2018; Sabatino et al. 2018). Indiscriminate or excessive use of these medications is not without consequence. Since the rapid increase of opioid usage occurred in the 1990's, the Centers for Disease Control and Prevention (CDC) reported over 640,000 deaths from overdose, including many of these resulting from misuse of prescribed opioids (Control CfD 2023b). Opioid prescribing habits among orthopedic surgeons are particularly relevant; over 8% of first-time opioid users undergoing an

orthopedic procedure become chronic users (Gil et al. 2019).

Recent literature has sought to determine whether opioid usage, despite the dependence risk, provided any benefit over opioid-sparing pain management techniques. A 2022 randomized control trial (Gazendam et al. 2022) compared standard opioid treatment with an opioid-free protocol following shoulder arthroscopy; the authors found no difference in pain scores between the two interventions at a 6-week follow-up. Furthermore, it has been demonstrated that patients undergoing either anatomical or reverse shoulder arthroplasty (RSA) who had used opioids preoperatively had reduced outcome measures and increased postoperative pain compared to patients with no history of opioid use (Morris et al. 2016; Al-Mohrej et al. 2023; Morris et al. 2015; Cheah et al. 2017; Grace et al. 2018; Thompson et al. 2019; Curtis et al. 2019; Mayer et al. 2019; Williams et al. 2019; Lu et al. 2020). Patients with a history of opioid use prior to surgery had lower American Shoulder and Elbow Surgeon (ASES) scores and range of motion, along with higher Visual Analog Scale (VAS) pain scores. Thus, there has been a current shift towards reducing opioid use and adopting a multimodal analgesia approach, using primarily over-the-counter analgesics (Gazendam et al. 2021).

4. EFFICACY OF LIPOSOMAL BUPIVACAINE IN SHOULDER SURGERY

Since the introduction of LB for pain control following shoulder surgery, numerous studies have demonstrated improved outcomes and patient satisfaction scores (Sabesan et al. 2017). In a randomized controlled trial (RCT) of 50 patients undergoing primary arthroscopic rotator cuff repair (RCR) for full-thickness rotator cuff tears, patients receiving LB exhibited lower VAS scores on day 1 and day 2, as well as lower cumulative scores over the five-day postoperative period compared to patients who did not receive LB in addition to their standard pain control management protocol. The LB group also consumed 64% less overall narcotics, evidenced by fewer narcotic pills consumed and fewer medication refills (Sethi et al. 2019). These findings suggest a potential for LB to contribute to a more comfortable and efficient recovery process.

Another RCT assigned 155 patients undergoing total shoulder arthroplasty (TSA) or RCR into three analgesic groups with administration of (Yoon et al. 2012) 133 mg of LB (Gramke et al. 2007), 266 mg of LB, or a (Vrancken et al. 2018) placebo, in addition to a standardized postoperative pain management protocol (M. A. Patel et al. 2020). The 133 mg LB group consumed 78% less opioids than those of the placebo group and were nine times more likely to be opioid-free during the 0-48 hours postoperative period, with no significant adverse effects. This highlights the opioid-sparing utility of liposomal bupivacaine as a single injection brachial plexus block supplementing a standard postoperative shoulder pain protocol.

These improved outcomes following the use of LB after shoulder surgery have sparked interest in understanding

the efficacy of LB in comparison to traditional pain management methods. In a recent RCT evaluating the brachial plexus blockade with LB plus bupivacaine (LB+B) compared with ropivacaine plus dexamethasone (R+D) during arthroscopic RCR, the LB+B group demonstrated a significant and sustained decrease in the “worst pain” score, opioid consumption, and overall benefit of analgesia score (OBAS) (Simovitch et al. 2022). Furthermore, in a prospective study comparing continuous ISB to regional LB combined with a single bolus ISB for postoperative pain control following primary shoulder arthroplasty, the LB group demonstrated significantly better Penn Shoulder Scores (PSS) and ASES scores (Sabesan et al. 2017). However, Subjective shoulder value (SSV), patient-reported pain levels, and satisfaction scores were comparable between groups at 2, 7, and 30 days postoperatively, with similar postoperative opioid use over 48 hours. Although numerous studies demonstrate improved postoperative pain, decreased opioid consumption, decreased length of hospital stay, and decreased utilization cost after shoulder surgery compared to other analgesic methods (i.e. non-liposomal agents, continuous interscalene catheter, standard ISB, opioids, etc.), conflicting evidence exists in the literature (Jindia et al. 2022; Mandava et al. 2021; Cohen 2012; Kirkness et al. 2016).

A systematic review of seven RCTs found that single-ISB treatment demonstrated decreased pain scores in the immediate postoperative period (0 to 8 hours) compared to local infiltration using LB following shoulder arthroplasty (Cohn et al. 2021). The opioid-sparing effect was inconclusive between the two groups. However, it is important to note that peak plasma levels of LB are reached at 10 to 36 hours postoperatively which may explain the difference in pain scores found within this study (Hu et al. 2013). Furthermore, the rebound pain effect of ISB initiates at 24 hours postoperatively (Abdallah et al. 2015). Thus, a longer follow-up period within this study may result in conflicting evidence compared to the author’s initial findings. However, other studies also report contradictory results regarding LBs opioid-sparing effect, hospitalization duration, and pain relief when compared to other non-liposomal analgesics for use in shoulder surgery (Kolade et al. 2019; Namdari et al. 2018; Schumaier et al. 2023; Abildgaard et al. 2017; Li et al. 2022).

Despite adequate pain control and patient satisfaction, further studies are needed to establish LB’s superiority over other analgesic methods. While considered cost-effective in postoperative pain management, future research should provide evidence of reduced financial burden on patients or healthcare systems compared to alternative analgesics (Kirkness et al. 2016; Chintalapudi et al. 2022; Lonza et al. 2023).

5. SAFETY AND ADVERSE EVENTS

The extensive investigation into the outcomes of utilizing LB following shoulder surgery has led to a well-characterized understanding of its safety and the frequency of adverse events. Common adverse effects following LB use include constipation, nausea, vomiting, headache, pyrexia,

hyperkalemia, dysgeusia, and respiratory insufficiency (Sabesan et al. 2017; M. A. Patel et al. 2020; Abildgaard et al. 2017; Kim et al. 2022). Furthermore, when compared to standard bupivacaine HCL, no additional risks regarding safety, wound and bone healing, cardiotoxicity, and side effect profile exists (Jindia et al. 2022; Baxter et al. 2013; Bergese et al. 2012; Bramlett et al. 2012; Ilfeld et al. 2015; Naseem et al. 2012; Viscusi et al. 2014). However, co-administration with other local antiseptics and anesthetics may increase the release of bupivacaine from liposomes (Chahar and Cummings 2012; Jindia et al. 2022).

Additionally, the existing literature has identified several risk factors that predispose a patient to inferior outcomes with LB following shoulder surgery. These include lack of patient education and postoperative pain expectations, history of opioid use, gender, prior surgery, history of cardiopulmonary compromise, and high American Society of Anesthesiologists Physical Status (ASA) score (Sabesan et al. 2023; Malige et al. 2020). Chronic pain has been proposed as one of these risk categories; however, conflicting studies exist regarding this finding and warrant further investigation (Namdari et al. 2018; Klug, Rivey, and Carter 2016; Weir et al. 2020). Factors that may result in poor pain control with LB are an area of particular interest for surgeons utilizing this emerging method, as it is a costly option (Beachler et al. 2017); therefore, understanding which groups may benefit from its use is imperative.

As more large-scale prospective studies investigate the utility of LB in shoulder surgery, further characterization of its adverse effects and risk factors, independent of other agents used in a multimodal approach, will occur. This ongoing research will provide surgeons with a clearer understanding of the safety and risks associated with LB as an approach to pain management after shoulder surgery.

6. CONCLUSION

Liposomal bupivacaine is a long-acting local anesthetic that has shown promise as an opioid-sparing alternative for pain management following shoulder surgery. Studies regarding its efficacy have demonstrated reductions in postoperative pain, opioid use, and length of hospitalizations over traditional pain management regimens. However, some literature has shown no clinical benefit and has described adverse effects including nausea, constipation, and respiratory depression. Certain patient populations may be more inclined to liposomal bupivacaine failure; thus, appropriate patient selection should be considered preoperatively.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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