Potential Utility of Liposome Bupivacaine in Orthopedic Surgery

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Abstract

Management of postsurgical analgesia is an important consideration in orthopedic procedures, including joint arthroplasty. Inadequate postsurgical analgesia is associated with increased hospital length of stay, delayed ambulation, and reduced exercise capacity.

In this article, we review the potential contribution of a prolonged-release liposomal formulation of bupivacaine as part of a multimodal analgesic regimen after orthopedic surgery.

Controlled studies across multiple surgical settings have demonstrated that, compared with placebo and bupivacaine HCl, liposome bupivacaine in a single administration provides postsurgical analgesia for up to 72 hours, delays use of rescue medication, and reduces postsurgical opioid consumption. Liposome bupivacaine has been well tolerated in clinical studies and has had a low rate of treatment-related adverse events. To date, there has been no signal of cardiac toxicity, chondrolysis, or delayed wound healing associated with liposome bupivacaine.

Approximately 5.5 million patients undergo orthopedic surgery in the United States each year, and more than 1 million of the procedures are total knee arthroplasty (TKA) or total hip arthroplasty.[1] From its 2010 level, demand for joint arthroplasty is expected to double by 2020 and quadruple by 2030.[2]

About half the patients who have major joint arthroplasty experience severe postsurgical pain.[3] Because postsurgical pain may persist for days or weeks, and inadequate treatment is associated with negative outcomes, achieving effective postsurgical analgesia is an important consideration.[4-7] Complications of inadequate postsurgical pain management include thromboembolic or pulmonary complications, development of chronic pain, and decrements in health-related quality of life.[4,8]

In patients who have orthopedic surgery, the inability to adequately control postsurgical pain has been associated with increased hospital length of stay (LOS), delayed time to ambulation, and reduced capacity for exercise.[9-12] A recent study involving 4709 patients who had hip or knee arthroplasty found that postsurgical pain relief was the second most highly correlated factor with respect to overall patient satisfaction (how well surgery met patient expectations was the most highly correlated factor),[13] suggesting that postsurgical analgesia should be a focus of surgical practice.

A prolonged-release liposomal formulation of the local anesthetic bupivacaine is now available. Bupivacaine liposome injectable suspension (Exparel; Pacira Pharmaceuticals, Inc., Parsippany, New Jersey) is indicated for administration into the surgical site to produce postsurgical analgesia.[14] In this article, we review evidence from clinical studies regarding the potential contribution of liposome bupivacaine to improving postsurgical pain management when used as part of a multimodal analgesic regimen in patients undergoing orthopedic surgery.

Postsurgical Pain Management in Orthopedic Surgery

Frequently Used Modalities

Analgesic modalities commonly used for perioperative pain management include central (eg, epidural),[4,10,15,16] central regional (eg, neuraxial),[4] peripheral regional (eg, peripheral nerve blocks, local/regional surgical site infiltration, intra-articular administration),[4,10,15,17-25] and intravenous (IV) patient-controlled analgesia.[4,10,25] These pharmacologic interventions may be augmented by nonpharmacologic modalities (eg, transcutaneous electrical nerve stimulation).[26]

Pharmacologic treatment options for perioperative pain management include opioids, local anesthetics, clonidine, ketamine, nonsteroidal anti-inflammatory drugs, acetaminophen, and calcium-channel blockers.[4,26-28] In TKA, "drug cocktails" (eg, combinations of ropivacaine, ketorolac, epinephrine, and clonidine) for regional or intra-articular injection can also provide effective immediate postsurgical analgesia.[25] Although

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opioids are the most commonly used analgesics for management of orthopedic perioperative pain,[25] their use is often associated with adverse effects (AEs), including constipation or ileus, nausea, sedation, dizziness, pruritus, urinary retention, and respiratory depression.[6]

Multimodal Analgesic Regimens for Postsurgical Pain Management

Current American Society of Anesthesiologists guidelines endorse use of multimodal analgesia, whenever possible, to provide effective management of acute perioperative pain.[4] Multimodal analgesia involves applying 2 or more agents with different mechanisms of action to achieve a synergistic effect, which allows each agent to be reduced in dose[4,28] and thereby may limit the risk and severity of dose-related AEs.[4,25,28]

Multimodal analgesia aims to reduce the risk for opioid-related AEs (ORAEs) and the impact of opioids on postsurgical milestones (eg, ambulation, discharge) and may reduce opioid consumption, with attendant reductions in ORAE risk.[29,30] Health economics studies have shown that postsurgical ORAEs are associated with increased hospital costs and LOS.[6] In a study using a national hospital database, development of an ORAE (vs no ORAE) in postsurgical patients was associated with mean increases of about $4700 in hospital costs and 3.3 days in LOS.[7] Reducing postsurgical opioid use may also help reduce the risk for opioid abuse, addiction, and diversion.[31-33]

One approach to reducing opioid use involves continuous or intermittent administration of local anesthetics by elastomeric pumps to extend duration of postsurgical analgesia.[34-36] However, use of elastomeric pumps has been associated with risk for AEs, including tissue necrosis, sloughing, wound infection, and chondrolysis.[37-40] In addition, AEs related to "dose dumping" (accidental delivery of excessive doses) have been reported.[40-44] Key issues that may negatively affect rehabilitation after orthopedic surgery include consistency and accuracy of analgesic delivery and the potential for motor block–induced muscle weakness, which may lead to falls and constrain ambulation.[45-47]

Liposome Bupivacaine

Description

Drug Delivery Technology. Liposome bupivacaine incorporates DepoFoam drug delivery technology (Pacira Pharmaceuticals, Inc.) to facilitate prolonged release of bupivacaine. This technology is based on creation of multivesicular liposome particles (diameter, 10-30 μm) with multiple aqueous chambers.[30,48] After administration into the surgical site, bupivacaine diffuses from chambers in the liposomal particles over time, providing analgesia and reduced opioid requirements for up to 72 hours.[29,30]

Indication, Mechanism of Action, Pharmacokinetics, and Dose/Administration. Liposome bupivacaine is indicated for single-dose administration into the surgical site to produce postsurgical analgesia in patients at least 18 years old.[14] Like other local anesthetics, liposome bupivacaine is thought to exert its pharmacologic effects by interacting with voltage-gated Na^+ channels on neural membranes to raise the threshold for electrical excitability, to slow nerve impulse propagation, and to reduce the rate of rise of the action potential.[14,49]

Liposome bupivacaine has dose-proportional pharmacokinetics.[50] Presence of a small amount of extra-liposomal bupivacaine in the formulation leads to a bimodal pharmacokinetic profile, with an initial peak serum concentration about 1 hour after administration, followed by a second peak within 12 to 36 hours (**Figure**).[50]

Maximum amount of liposome bupivacaine approved for single administration is 266 mg (packaged as 20 mL of a 1.3% solution). However, product labeling includes safety data associated with doses of 532 mg or less.[14] The appropriate volume to be used should be based on the amount required to cover the surgical area. Liposome bupivacaine may be expanded with preservative-free normal (0.9%) sterile saline to a total volume of 300 mL: 20 mL liposome bupivacaine plus 280 mL or less diluent, with final concen-

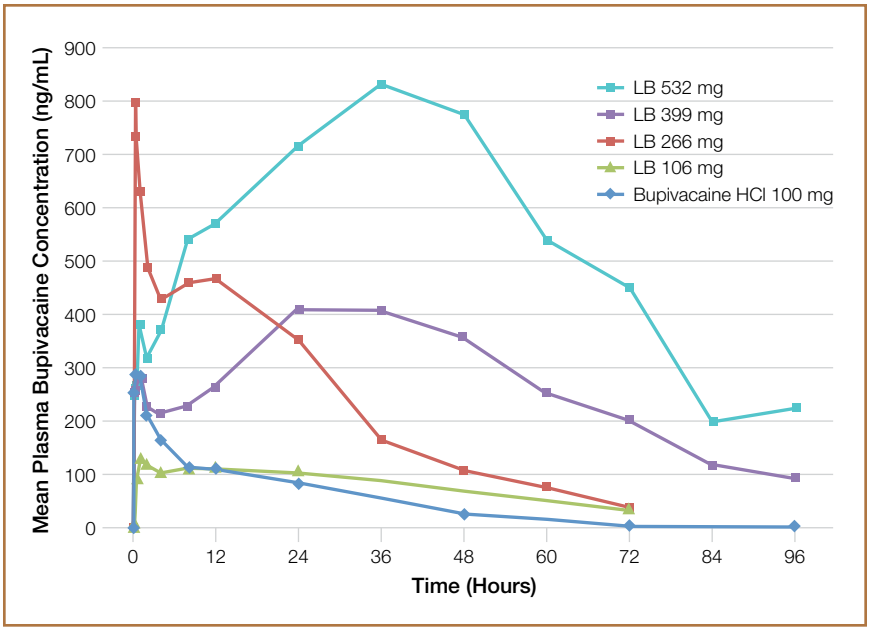

Figure. Plasma bupivacaine concentration versus time for liposome bupivacaine 106, 266, 399, and 532 mg and bupivacaine HCl 100 mg. Abbreviation: LB, liposome bupivacaine. Reprinted with kind permission from Springer Science and Business Media and Springer International Publishing Switzerland/*Clinical Drug Investigation*, volume 33, 2013, pages 109-115, Pharmacokinetic Profile of Liposome Bupivacaine Injection Following a Single Administration at the Surgical Site, DeeDee Hu, Erol Onel, Neil Singla, William G. Kramer, Admir Hadzic, Figure 1, © Springer International Publishing Switzerland 2012.[50]

tration of 0.89 mg/mL (1:14 by volume).[14]

A 25-gauge or larger bore needle should be used to slowly inject liposome bupivacaine into soft tissues of the surgical site, with frequent aspiration to check for blood to minimize risk for intravascular injection.[14] Total volume used and fraction injected in specific regions of the surgical site depend on the procedure. For example, a TKA study used 266 mg diluted to a total volume of 60 mL, with 8 mL infiltrated to the area around the medial capsule, 8 mL around the lateral capsule, 12 mL around the posterior capsule, 8 mL around the peripatellar area, 12 mL into the capsulotomy incision, and 12 mL into the subcutaneous tissue on each side of the incision.[51]

Efficacy

Multiple Surgical Settings. The efficacy of liposome bupivacaine, either alone or as a component of a multimodal analgesic regimen, has been evaluated in a series of 10 phase 2 and 3 studies (8 active-controlled, 2 placebo-controlled) involving 823 patients undergoing TKA, bunionectomy, hemorrhoidectomy, inguinal hernia repair, or mammoplasty.[52] Patients received a single liposome bupivacaine dose ranging from 66 to 532 mg.[52]

Combined analyses of efficacy data from these studies found that liposome bupivacaine–based multimodal analgesic regimens produced postsurgical analgesia for up to 72 hours, increased time to first use of opioid rescue medication after surgery, and reduced total amount of postsurgical opioid consumption versus placebo.[52]

Compared with standard of care, liposome bupivacaine has been shown to provide effective analgesia in open-label studies in patients undergoing open colectomy,[53] laparoscopic colectomy,[54] and ileostomy reversal,[55,56] as reflected in assessments of postsurgical opioid consumption, LOS, and hospital costs. It has also been studied when administered by infiltration into the transversus abdominis plane (TAP) in patients having laparoscopic prostatectomy and open abdominal hernia repair.[57,58]

Orthopedic Surgery. In a phase 2 randomized, double-blind, dose-ranging study, TKA patients (N = 138) received bupivacaine HCl 150 mg or liposome bupivacaine 133, 266, 399, or 532 mg administered by local infiltration into the capsulotomy incision and on either side of the incision before wound closure.[51] Postsurgical rescue analgesia was available to all patients. Cumulative pain intensity scores with activity (primary efficacy measure) were not statistically different between liposome bupivacaine groups and the bupivacaine HCl group through postoperative day 4. Mean scores in the liposome bupivacaine 266-, 399-, and 532-mg groups were numerically lower than for those treated with bupivacaine HCl on postoperative days 2 to 5, with all doses of liposome bupivacaine having a statistically significant lower pain score at rest on day 5. There were no statistically significant differences across treatment groups with respect to total amount of postsurgical opioids used.

In a phase 3 randomized, double-blind study of TKA patients (N = 245), liposome bupivacaine 532 mg administered into the surgical site was compared with bupivacaine HCl 200 mg for postsurgical analgesia.[52] Rescue analgesia was available to all patients. No statistically significant between-group differences were found with respect to postsurgical cumulative pain scores through 72 hours (primary efficacy endpoint).

In a single-center retrospective TKA study, postsurgical outcomes in a patient cohort that received intraoperative periarticular infiltration with liposome bupivacaine 266 mg (n = 65) were compared with a cohort that received infiltration with a combination of ropivacaine 400 mg, morphine 5 mg, and epinephrine 0.4 mg (n = 85).[59] Patient-reported postsurgical pain scores were similar in the 2 treatment groups during the first 24 hours after surgery and at discharge. Mean (SD) pain scores during hospitalization after the first 24 hours until discharge were significantly ($P = .04$) higher in the liposome bupivacaine group, 4.9 (1.4), than in the periarticular group, 4.4 (1.6). There was no significant difference between the 2 treatment groups in postsurgical opioid use. The study demonstrated no advantage to using liposome bupivacaine injections with respect to pain relief, but it was a retrospective review in which pain scores were obtained from electronic medical records. It is essential that liposome bupivacaine be compared with intra-articular injections in well-designed randomized trials.

Another single-center, matched-cohort TKA study (N = 200) compared a liposome bupivacaine regimen with femoral nerve block.[60] Compared with patients who received femoral nerve block, patients who received liposome bupivacaine reported lower pain intensity scores after surgery and had shorter LOS, reduced costs, and improved knee flexion at follow-up.[60]

Results from 2 other studies were presented at the 2014 meeting of the American Academy of Orthopaedic Surgeons (AAOS). One was a single-center, matched-cohort TKA study (N = 72) comparing infiltration of a single dose of liposome bupivacaine into the surgical site with continuous femoral nerve block.[61] The 2 treatment groups had similar mean postsurgical pain intensity scores on a 0-to-10 visual analog scale, 1.8 for liposome bupivacaine and 2.3 for continuous nerve block (P = NS), but total amount of postsurgical opioids (hydrocodone-equivalent milligrams) was significantly ($P < .0001$) less in the liposome bupivacaine group (82 vs 177 mg).

The other study presented at the AAOS meeting was a larger, prospective case–control study comparing outcomes between 1000 patients who had total joint arthroplasty (TJA) with liposome bupivacaine and 1000 control patients who had TJA without liposome bupivacaine.[62] For the control and liposome bupivacaine cohorts, respectively, mean postsurgical pain intensity scores were 2.41 and 1.98 ($P < .0001$), mean LOS was 2.83 days and 2.66 days ($P < .02$), and incidence of falls was 1.0% and 0.2% ($P = .02$). Average per-patient costs were $1246 lower in the liposome bupivacaine cohort.

A pivotal phase 3 placebo-controlled study compared liposome bupivacaine 106 mg with placebo in patients undergoing bunionectomy (N = 193).[5] Rescue medication was available to all patients. Cumulative pain scores were significantly ($P = .0005$) lower in the liposome bupivacaine group (125) than in the placebo group (146) through 24 hours after sur-

gery (primary efficacy measure) and significantly (P = .0229) lower (197 vs 220) through 36 hours. Median time to first use of rescue opioids was delayed in favor of the liposome bupivacaine group (7.2 vs 4.3 hours; P < .0001). Mean total number of opioid tablets used within 24 hours after surgery was also significantly lower (3.8 vs 4.7; P = .008), and a larger percentage of patients in the liposome bupivacaine group avoided opioid use altogether through 24 hours (7% vs 1%; P = .04).

Efficacy data for liposome bupivacaine appear promising for relief of pain after joint arthroplasty and other orthopedic procedures but have their limitations. First, no randomized trials have compared liposome bupivacaine with locally injected pain medications (intra-articular injections in TKA or hip arthroplasty). As these injections are quite common now, such analyses are essential. Second, cost-effectiveness studies are needed for orthopedic procedures. Third, most of the published studies were sponsored by the manufacturer of liposome bupivacaine—a situation that raises questions about potential bias. Non-industry-sponsored randomized trials assessing efficacy, safety, and cost-effectiveness are needed.

Safety

Local anesthetics, including liposome bupivacaine, have the potential for central nervous system (CNS) or cardiac toxicity resulting from excessive systemic absorption or inadvertent IV administration.[63] However, reported serious CNS or cardiac-related AEs are rare.[63,64]

AE Profile. Safety data from 10 phase 2 and 3 studies involving 823 patients who received liposome bupivacaine were evaluated.[65] Of these patients, 545 received a dose of 266 mg or less (maximum dose approved by the US Food and Drug Administration [FDA]). Liposome bupivacaine was generally well tolerated. Reported AE incidence was 62% (liposome bupivacaine), 75% (bupivacaine HCl), and 43% (placebo). More than 90% of reported AEs were mild or moderate. The most frequently reported AEs were nausea, constipation, and vomiting (liposome bupivacaine, bupivacaine HCl) and nausea, dizziness, and vomiting (placebo).

Serious AEs were reported in 22 (2.7%) of the 823 patients in the liposome bupivacaine group, 24 (5.4%) of the 446 in the bupivacaine HCl group, and 2 (1.1%) of the 190 in the placebo group.[65] None of the serious AEs in the liposome bupivacaine and placebo groups were considered treatment-related. Six patients in the bupivacaine HCl group had treatment-related serious AEs (hypoglycemia, arthrofibrosis, hemarthrosis, joint swelling, scar, knee arthroplasty).

Cardiac Safety. Possible cardiac effects associated with liposome bupivacaine were evaluated with data from studies conducted during the clinical development program.[66] One hundred thirty-eight patients participated in the phase 2 safety and efficacy study in TKA. In these patients, a consistent change in mean heart rate (range, +12.2 to +16.5 beats per minute) was found across all liposome bupivacaine doses and with bupivacaine HCl. No clinically relevant changes from baseline in mean electrocardiographic parameters, including QTcF interval (QT interval adjusted using Fridericia's correction formula), were found. In another analysis,[67] liposome bupivacaine administered in a single subcutaneous dose (266, 399, 532, or 665 mg) to healthy volunteers did not prolong (vs placebo) QTc interval.

Wound Healing. The potential effects of liposome bupivacaine on wound healing were evaluated with results from 10 phase 2 and 3 studies.[68] The assessments, which varied across studies, included clinicians' overall satisfaction with patient wound healing, wound status assessment (categories included erythema, drainage, edema, and induration), and wound scarring (categories included pigmentation, height, pliability, and vascularity). Clinician-assessed scores reflected high satisfaction with wound healing overall. There were few statistically significant differences in wound status assessments between liposome bupivacaine and the comparators and no statistically significant differences in scarring between liposome bupivacaine and bupivacaine HCl.

The potential of liposome bupivacaine to have adverse intra-articular effects was assessed with drainage samples from patients (n = 23) who had TKA and received liposome bupivacaine (133, 266, 399, or 532 mg) or bupivacaine HCl (150 mg) by wound infiltration near the intra-articular space.[51,65] Only small amounts of bupivacaine were present in drainage fluid collected for 12 hours after liposome bupivacaine administration, comparable to bupivacaine HCl administration.[65] Currently, the product is not approved for intra-articular use.

Compatibility With Diluents, Other Medications, and Implant Materials

Liposome bupivacaine may be expanded up to a ratio of 1:14 by volume (to a final total volume of 300 mL or a concentration of 0.89 mg/mL) using preservative-free normal (0.9%) sterile saline for injection.[14] It has also been shown in vitro to be compatible with lactated Ringer solution as a diluent.[69]

Liposome bupivacaine should not be admixed with other medications before administration.[14] No formal drug–drug interaction studies have been conducted with liposome bupivacaine, but it has been shown in vitro to be compatible with epinephrine solutions, with certain anti-infective medications (eg, bacitracin, gentamicin, cefazolin, cefuroxime), with certain analgesics (eg, ketorolac, morphine), with an antihypertensive medication (clonidine), with an antihemorrhagic medication (tranexamic acid), and with certain corticosteroids (eg, methylprednisolone, triamcinolone acetonide). These medications may be coadministered in the same location as liposome bupivacaine.[69]

Topical antiseptics (eg, povidone iodine) may be used in surgical procedures involving liposome bupivacaine as long as they are not directly mixed with liposome bupivacaine and are allowed to dry before it is administered. If a topical antiseptic is used for wound irrigation, the wound should be rinsed clear before liposome bupivacaine administration.[14,69]

Liposome bupivacaine may be coadministered into the same surgical site immediately *after* bupivacaine HCl as long as the dose ratio of liposome bupivacaine to bupivacaine HCl is 2:1 or higher. Because of the prolonged-release pharmacokinetic profile of liposome bupivacaine and the potential for increased bupivacaine exposure, bupivacaine HCl should not

be administered within 96 hours after administration of liposome bupivacaine.[14,69]

In vitro coincubation studies of liposome bupivacaine and other local anesthetics, including ropivacaine, lidocaine, and mepivacaine, have found rapid release of free bupivacaine from the liposome matrix. Therefore, after giving any of these other local anesthetics, surgeons should wait at least 20 minutes before administering liposome bupivacaine into the same area.[14,69]

In vitro studies have shown that liposome bupivacaine is compatible with a wide range of commonly used implant materials, including polypropylene, expanded polytetrafluoroethylene, stainless steel, titanium, and smooth- and textured-type silicone.[69]

Investigational Use and Ongoing Studies

A phase 2 randomized, double-masked, dose-escalating/deescalating study was conducted to evaluate the efficacy, safety, and pharmacokinetics of liposome bupivacaine (155, 199, or 310 mg) in comparison with bupivacaine HCl 125 mg for ankle nerve block in patients undergoing bunionectomy (N = 58).[70] The study medication was injected into 3 sites to reach the posterior tibial, sural, deep peroneal, superficial peroneal, and saphenous nerves. Pharmacokinetic exposure was higher for liposome bupivacaine than for bupivacaine HCl, as reflected by a significantly greater area under the curve, lower C_{max} (maximum serum concentration), and longer mean half-life. Mean pain intensity scores were lower in the bupivacaine HCl group than in each liposome bupivacaine group the first 12 hours after surgery. However, the liposome bupivacaine 310-mg group had similar or lower scores than the bupivacaine HCl group from 12 to 96 hours after surgery. The most common AEs in the liposome bupivacaine group were gastrointestinal and not treatment-related.[70]

The efficacy and safety of liposome bupivacaine, administered as a femoral nerve block for postsurgical analgesia, were assessed in a phase 2/3 manufacturer-sponsored, placebo-controlled, multicenter, randomized, double-blind 2-part study (NCT01683071)[71] in 280 TKA patients.[71,72] Part 2 of the study, comparing liposome bupivacaine 266 mg (n = 116) and placebo (n = 116), met its primary endpoint, demonstrating statistical significance in favor of liposome bupivacaine for cumulative pain scores over 72 hours ($P < .0001$), with decreased opioid use ($P < .05$) and a safety profile similar to that of placebo.[72]

Other ongoing investigator-sponsored studies in orthopedic populations include comparisons of liposome bupivacaine and bupivacaine HCl for ultrasound-guided periarticular hip infiltration in hip arthroplasty (NTC01917191),[73] as femoral nerve block in TKA (NCT01977339),[74] and as interscalene brachial plexus block in arthroscopic shoulder surgery (NCT01977352).[75] The primary efficacy outcome measure in these studies was postsurgical opioid use.[73-75]

Health Economics

A series of phase 4 health economics studies was conducted for gastrointestinal surgeries, including open colectomy, laparoscopic colectomy, and ileostomy reversal.[53-56,76] These studies, of similar design, showed that a liposome bupivacaine–based multimodal analgesic regimen was associated with reduced opioid use, shorter hospital LOS, and lower hospitalization costs in comparison with a traditional opioid-based regimen.[53-56] Although pooled analysis of these studies showed a cost savings of more than $2000 per patient and an LOS decrease of 1.4 days,[76] all were conducted in the gastrointestinal surgery setting. Studies are needed to fully assess the economic benefits associated with liposome bupivacaine in the orthopedic surgery setting.

Conclusion

Liposome bupivacaine represents a potentially important contributor to multimodal analgesic regimens used to manage postsurgical pain. Liposome bupivacaine has demonstrated efficacy in providing prolonged postsurgical analgesia and reducing postsurgical opioid use in most surgical settings studied. Additional data from health economics studies in gastrointestinal surgery suggest liposome bupivacaine–based multimodal analgesic regimens may also contribute to reductions in hospital LOS and hospitalization costs. Non-industry-sponsored trials are needed to answer these crucial questions in orthopedic surgery settings. Nevertheless, data on the safety and efficacy of liposome bupivacaine for postsurgical analgesia continue to accumulate, and liposome bupivacaine appears to be a feasible therapeutic option for managing postsurgical pain in orthopedic surgery.

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