SCIENTIFIC ARTICLE

Will the Use of Intraoperative Liposomal Bupivacaine During Thumb Carpometacarpal Arthroplasty Decrease Postoperative Use of Opioids? A Prospective Randomized Study

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Purpose This study evaluated the use of intraoperative local injection of liposomal bupivacaine to decrease opioid use in the early postoperative period for patients undergoing outpatient thumb carpometacarpal joint arthroplasty.

Methods A prospective, randomized, controlled, single-blinded study was designed to compare 2 groups of patients for opioid use, pain scores, and nonopioid pill consumption within 5 days after surgery. The investigational group received an intraoperative injection of 10 ml (133 mg) liposomal bupivacaine. The control group received no local anesthetic. All patients were anesthetized with a standardized supraclavicular nerve block and were prescribed equal amounts of oral narcotic analgesic. Outcomes were assessed by collecting the data from postoperative patient-reported diaries.

Results The experimental group reported a significantly lower total opioid consumption for the 5 days after surgery. Daily opioid use, as measured by both opioid pill equivalent count and morphine milligram equivalent in addition to postoperative pain scores and nonopioid pill consumption, was not different between groups.

Conclusions Intraoperative injection of liposomal bupivacaine was shown to decrease total opioid intake during the 5 days after thumb carpometacarpal arthroplasty. *(J Hand Surg Am. 2022;47(6):586.e1-e8. Copyright © 2022 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic II.

Key words Analgesia, carpometacarpal, liposomal bupivacaine, opioid, postoperative pain.

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UPPER-EXTREMITY SURGERY can cause considerable pain, affecting patient satisfaction and prolonging rehabilitation.[1–3] Physicians must provide adequate pain relief while minimizing the side effects, risk of dependence and possible abuse associated with opioid consumption.[4] Patients take opioid medication for an average of 3.1 days after most upper-extremity procedures but no longer than postoperative day 3 for many hand and wrist

procedures.[5] Patients undergoing surgeries with bone involvement consume more pills than those undergoing soft tissue procedures.[3]

Growing concerns about narcotic use have resulted in increased attention to alternative treatment methods. Kelley et al,[6] after a systematic literature review, recommended a patient-centered pain control strategy that included preoperative assessment of the risk of postoperative pain, inclusion of nonnarcotic medications, and the use of postoperative infusion catheters in cases of potential severe pain. Another direction of investigation involves modifying local anesthetic agents to prolong their duration of effectiveness and reduce toxicity. Lipid-based formulations of local anesthetics with liposomes or microemulsions can provide these benefits. Only liposomal bupivacaine (LB) (Exparel, Pacira Pharmaceuticals, Inc) has been approved for clinical use at this time.[7] Liposomal bupivacaine is a suspension composed of bupivacaine carried by liposomes. This preparation provides a slower diffusion of medication than the aqueous based solution of bupivacaine hydrochloride (HCl). Liposomal bupivacaine has the theoretical benefit of providing prolonged postoperative pain relief and decreasing opioid use through postoperative days 2 and 3.[8] Several studies have evaluated LB in patients undergoing hand surgery with mixed results.[9–12] The differences in injection techniques and approaches to pain assessment could contribute to the disparate results. Because of its limited distribution pattern, LB requires more injection sites than other local anesthetics. The importance of optimal LB infiltration into the areas of highest nerve density was advocated in recent studies.[8,13]

The purpose of this study was to test the hypothesis that intraoperative infiltration of LB, with a standardized technique, would provide optimal pain control and decrease postoperative opioid use for patients undergoing thumb carpometacarpal (CMC) joint arthroplasty.

MATERIALS AND METHODS

This prospective, randomized, controlled single-blinded study was conducted at a hand care practice by a single surgeon. Institutional review board approval was obtained. No industry support was solicited or received. We enrolled surgical candidates 18 years or older who were scheduled for elective, outpatient thumb CMC joint arthroplasty. Carpal tunnel release and metacarpophalangeal joint capsulodesis were the only concomitant procedures allowed. Patients were excluded from the study if they had a history of drug/alcohol abuse, any opioid use within 3 days prior to surgery, a history of known allergy to the study drugs, or existing medical comorbidities that were expected to interfere with postoperative recovery. Fifty-four consecutive patients recommended for CMC arthroplasty were screened for study inclusion. Two were not eligible based upon study criteria, 5 declined to participate, and 6 could not participate because their surgery was scheduled after our study cohort of 40 patients had been filled. Informed consent was obtained from patients who met the inclusion criteria and agreed to participate in the study. Participants were randomly assigned to experimental or control study groups and remained blinded throughout their study participation. No incentives were offered for participation.

All participants received a preoperative supraclavicular nerve block that was standardized to the type, quantity, and concentration of medication used and to the injection procedure (bupivicaine 0.75% 30 ml mixed with chloroprocaine 3% 20 ml and epinephrine 1:400 k, 40 ml of the 50 ml solution was used). No additional pain relief adjuncts were administered. All patients had a trapezial excision, ligament reconstruction, and tendon interposition performed by the primary investigator. The incision was made through a radiopalmar Wagner approach that included release of the first dorsal compartment. The trapezium was excised in 1 piece, and the entire flexor carpi radialis tendon was harvested from a volar forearm incision 8 cm proximal to the wrist flexion creases. The suspension was performed by passing the flexor carpi radialis tendon through a drill hole in the base of thumb metacarpal, suturing it to itself at the base of the index metacarpal and sewing the remainder of the tendon into a ball that was secured into the space left by the excised trapezium.

Patients randomized to the experimental group received an intraoperative local infiltration of 20 ml of a solution composed of 10 ml (133 mg) of LB that was diluted with 10 ml of normal saline. After trapezium excision, the first half of the solution, 10 ml, was slowly injected through the incision into the posterior aspect of the capsule and around the capsular space dorsally and palmarly using a moving needle technique. Injections were done 1.0 cm to 1.5 cm apart, to ensure overlapping analgesic coverage. Care was taken to avoid injection into the radial artery or around the median nerve. The second half of the LB solution was administered into the skin edges and subcutaneous tissue around the repair site after capsule closure. A small amount was injected into the

TABLE 1. Patient Demographics

Patient Demographics	Experimental N = 19	Control N = 19	Total N = 38
Sex (M/F)	10/9	5/14	15/23
Age (mean)	65 y (range 48–78)	65 y (range 55–80)	65 y (range 48–80)
Body mass index (mean)	30 (range 22–44)	30 (range 21–44)	30 (range 21–44)
Tobacco use (Never/former/current)	9/6/4	13/6/0	22/12/4
Hyperlipidemia	7	6	13
Hypertension	3	5	8
Diabetes mellitus	2	2	4
Cervical stenosis	1	2	3
Rheumatoid arthritis	0	2	2
Depression	2	0	2
Fibromyalgia	1	0	1
Gout	1	0	1
Surgery length (mean)	45 min (range 32–62)	48 min (range 32–81)	46 min (range 32–81)
Tourniquet time (mean)	45 min (range 32–61)	47 min (range 30–79)	46 min (range 30–79)

forearm incision that was used to harvest the flexor carpi radialis tendon. The control group received no intraoperative anesthetic injection. All patients in both groups received a postoperative prescription for oral hydrocodone-acetaminophen 5 mg/325 mg, 20 tablets (or morphine equivalent in case of allergy). Following hospital discharge, participants were asked to complete a medication diary for both opioid and nonopioid analgesics consumption. The medication taken, dose, and time of administration were recorded. Every 12 hours, patients completed a 10-point visual analog pain score (0 = no pain, 10 = worst imaginable pain). All data were recorded through postoperative day 5. The patients brought medication and pain diaries to the first postoperative visit. At that time, any adverse events (AEs) related to the drug used in the study were evaluated and recorded. The number of opioid pills used was collected from the patient's medication log and converted to morphine milligram equivalent (MME). The MME was then converted back to a pill count equal to pills of the strength hydrocodone 5 mg/325 mg.

An appropriate sample size was estimated using a 2-sided 2-group *t* test. A sample size of 17 patients per group was determined to be sufficient to detect a difference of 1 pill per day, with 80% power and an alpha error of 0.05, assuming normal distribution and a standard deviation of 0.80.

The sample size required to detect a significant difference in the secondary outcomes of pain level and nonopioid medication was calculated using Wilcoxon rank sum test (Mann-Whitney U test) and indicated that only 15 patients per group were required to detect a significant difference. Considering a possible 15% withdrawal rate, we felt that a total of 40 patients, 20 in each group, should be enrolled. Due to skewed data distribution, nonparametric methods were used to compare the experimental and control groups. Pairwise comparison was made using the Kruskal-Wallis test. The Mann-Whitney U test was used to compare both arms for total number of days, morphine pill equivalent, MME, and nonopioid pills used.

RESULTS

A total of 40 patients were enrolled (August 2019–March 2020): 20 to the control group and 20 to the experimental group. Two patients were excluded from the study: 1 participant confirmed opioid use within 3 days of surgery, and 1 participant violated the prescribed postoperative pain medication recommendations by taking a second nonprescribed opioid drug. Ultimately, 19 patients in each group successfully completed the study. A complete data set was collected for all patients. The primary diagnosis for all participants was osteoarthritis of the thumb CMC joint. Comorbidities of relevance and procedure type are presented in Tables 1 and 2. There were no AEs or cases of allergic reactions to study drugs.

The primary study objective was to compare postoperative total opioid consumption as measured by oral opioid pill equivalent (hydrocodone-acetaminophen 5 mg/325 mg) (Fig. 1) and MME starting

TABLE 2. Procedure Type

Procedure Type	Total N = 38
LRTI with trapeziectomy	23
LRTI with trapeziectomy and partial trapezoidectomy	10
LRTI with trapeziectomy and CTR	2
LRTI with trapeziectomy and thumb MCP capsulodesis	1
LRTI with trapeziectomy and partial trapezoidectomy & CTR	1
LRTI with trapeziectomy and partial trapezoidectomy and thumb MP capsulodesis	1

CTR, carpal tunnel release; LRTI, ligament reconstruction tendon interposition; MCP, metacarpophalangeal.

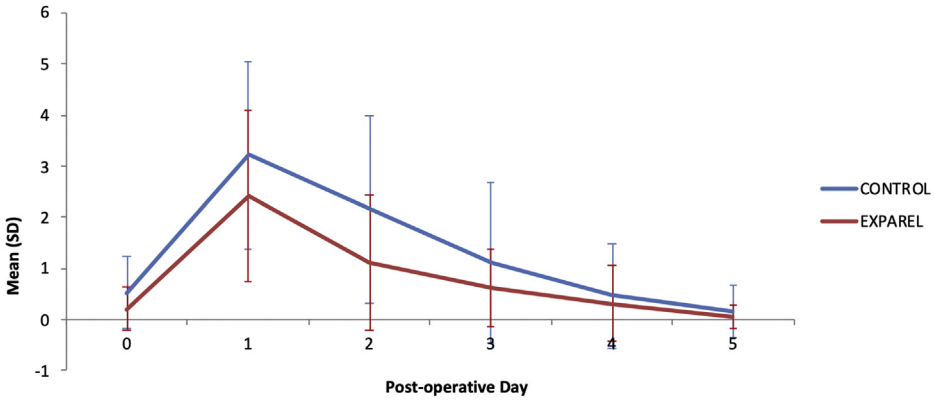

FIGURE 1: Postoperative oral opioid pill equivalent count.

on the day of surgery through postoperative day 5. A statistically significant difference between the experimental and control groups was observed for total opioid consumption. The median total 5-day postoperative opioid pill equivalent count was 8 in the control group and 5 in the experimental group ($P < .05$). The total median MME was significantly different ($P < .05$), with the control group using 40 MME and the experimental group using 30 MME. Daily opioid use, as measured by both opioid pill equivalent count (Table 3) and MME, was not different between groups.

Two subjects from the experimental and 1 from the control group had no opioid use throughout the recovery period.

Secondary outcomes included postoperative visual analog pain scores and nonopioid pill count. Patients in the experimental group reported lower pain levels, especially on the second day after the surgical intervention; however, the difference was not statistically significant ($P = .075$) (Fig. 2). It is notable that nonopioid pill consumption was higher over the course of the study in the control group, even though this group also reported increased opioid use (Fig. 3). Median values for postoperative pain scores and nonopioid pill consumption were not statistically different between the groups (Tables 4, 5). Over-the-counter pain relievers included ibuprofen 200 mg (22 patients), acetaminophen 500 mg (9 patients), and naproxen 200 mg (5 patients). Of those, 21 participants used a single drug, 7 a combination of 2 or more, and 10 patients none.

DISCUSSION

Liposomal bupivacaine effectiveness remains controversial. Different administration techniques, nonstandardized dosage, and a variety of control group strategies may be the cause for inconsistent results of previous studies.[9–11,14] LB was frequently included as a component of a multimodal treatment plan prescribed by various specialists for a variety of procedures. This mixture of variables makes it difficult to determine LB efficacy when given alone.[6,15,16] Thompson et al[12] compared pain control with an indwelling interscalene catheter to a wound site injection of a LB mixture including bupivacaine, morphine, and ketorolac after total elbow

TABLE 3. Postoperative Opioid Pill Equivalent Count (Median, IQR*)

Postoperative Day	Experimental	Control	*P* Value
0	0 (0–0)	0 (0–1)	.132
1	3 (1–4)	3 (2–4)	.213
2	1 (0–2)	2 (1–3)	.06
3	0 (0–0)	0 (0–2)	.503
4	0 (0–0)	0 (0–1)	.666
5	0 (0–0)	0 (0–0)	.532
Total	5 (2–7)	8 (3–10)	.046

*Values in parentheses are the interquartile ranges (IQR) associated with the median values.

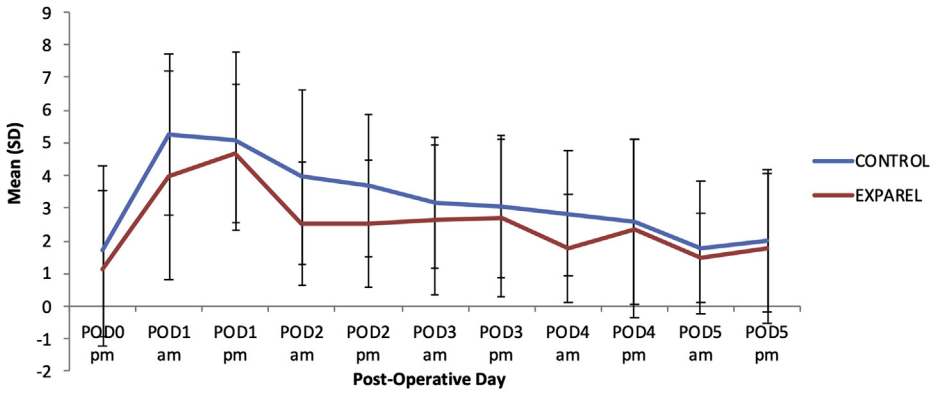

FIGURE 2: Postoperative pain levels (Visual Analog Pain Score, q 12 h). VAS, Visual analog scale; POD, post-operative day.

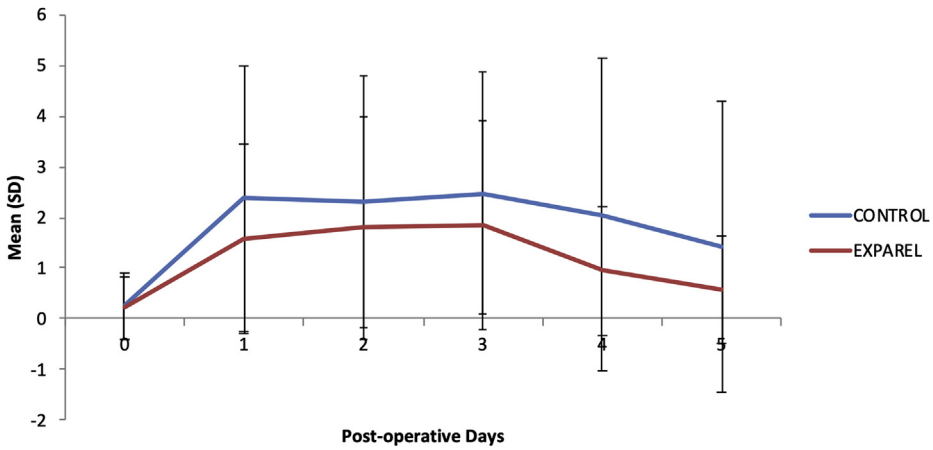

FIGURE 3: Postoperative nonopioid pill count.

arthroplasty. Narcotic consumption was higher in the LB group on the first day after the surgery, but cumulative use at 12 weeks was less. Liposomal bupivacaine was also shown to have significantly fewer complications in comparison to the catheter group. Another obstacle to comparing efficacy of injected anesthetics is administered dosage differences between the groups.[14] Dale et al[11] studied 20 ml (266 mg) LB versus 15 ml (75 mg) bupivacaine HCl for early postoperative pain control following CMC arthroplasty or proximal row carpectomy surgeries. Comparison of pain control efficacy provided by the 2 different products is complicated because the onset and duration of action are different. Moreover, there

TABLE 4. Postoperative Pain Levels Using a Visual Analog Pain Score (Median, IQR*)

Postoperative Day	Experimental	Control	*P* Value
0 PM	0 (0–1)	0 (0–3)	.402
1 AM	4 (1–6)	5 (3–8)	.191
1 PM	4 (3–7)	5 (3–8)	.488
2 AM	2 (1–4)	4 (2–6)	.123
2 PM	2 (1–4)	4 (2–5)	.075
3 AM	2 (0–4)	3 (2–5)	.385
3 PM	2 (1–4)	3 (1–4)	.563
4 AM	1 (0–3)	3 (2–4)	.109
4 PM	2 (0–4)	2 (1–4)	.686
5 AM	1 (0–2)	1 (0–2)	.954
5 PM	2 (0–2)	1 (0–4)	.751
Average	2.45 (1–4)	2.9 (1.7–4.5)	.234

*Values in parentheses are the interquartile ranges (IQR) associated with the median values.

TABLE 5. Postoperative Nonopioid Pill Count (Median, IQR*)

Postoperative Day	Experimental	Control	*P* Value
0	0 (0–0)	0 (0–0)	.672
1	2 (0–2)	2 (0–4)	.35
2	1 (0–4)	1 (0–4)	.503
3	2 (0–4)	2 (0–4)	.384
4	0 (0–2)	1 (0–3)	.331
5	0 (0–1)	0 (0–1)	.478
Total	6 (0–12)	8 (3–18)	.212

*Values in parentheses are the interquartile ranges (IQR) associated with the median values.

are no consistent guidelines on LB volume recommended for local administration in hand surgery. Recommended doses range from 5 ml to 20 ml. In the above-mentioned study, the authors used 20 ml LB, whereas Alter et al[9] used 10 ml LB after distal radius fracture fixation. Ketonis et al[10] administered 5 ml LB for trigger finger release. In our study, we found that a dose of 10 ml was sufficient for adequate analgesia and was associated with improved postoperative pain tolerance in CMC arthroplasty.

Liposomal bupivacaine has shown a favorable safety profile and is well-tolerated for local use. Portillo et al[17] conducted a systematic review of 6 prospective studies comparing LB with bupivacaine HCl or placebo. The most frequent AE reported was nausea, and bupivacaine HCl showed a higher incidence in contrast to the LB group. Viscusi et al[15] pooled safety data for 823 patients in 10 randomized studies. AEs were reported with the following frequencies: 43% of placebo, 62% of LB, and 75% of bupivacaine HCl. Most side effects were mild to moderate, and only 3.3% (for LB) were treated for nausea, vomiting, or constipation. Baxter et al[18] analyzed LB impact on wound healing in 10 controlled clinical trials. The incidence of local AEs (skin and subcutaneous tissue disorders) was similar in the placebo (5%), LB (9%), and bupivacaine HCl (12%) treatment arms. There were no relevant differences in scarring, drainage, or infections. The authors concluded that LB at doses up to 532 mg given via local administration has no clinically evident impact on wound or bone healing across different surgical models.

Studying acceptable concentration and drug interaction when used in combination with regional nerve blocks would also help to set the safety dosage limitations. Our study followed the manufacturer's recommendation that a ratio of 2:1 plain bupivacaine

to LB not be exceeded: 225 mg of bupivacaine was used in the regional block, and 133 mg of LB was used for surgical site infiltration.

The literature also supports LB efficacy for postsurgical analgesia. Ten local wound infiltration studies were assessed by Bergese et al.[14] The key measures included pain score, first rescue opioid medication use and total amount, as well as patient satisfaction. The higher doses of LB were associated with lower cumulative pain compared to other groups. A significant difference was found in median time to first postoperative opioid use: 9.3 hours with LB versus 6.4 hours with bupivacaine HCl and 3.6 hours with placebo. The proportion of patients avoiding opioid use and total consumption was also significantly lower in favor of LB.

The pharmacokinetic profile of LB given at the surgical site is well-established.[19] An initial plasma bupivacaine concentration peak is recorded at 1 hour after administration, whereas the remainder of LB is encapsulated in liposomes, delivering therapeutic levels of bupivacaine over 12 hours to 36 hours. This manner of tissue diffusion is the main advantage over bupivacaine HCL, allowing the prolonged analgesia where placed.

Cost effectiveness is another important factor. Even though LB is an additional expense, the price of the drug is not the only factor associated with the treatment cost benefit. Length of hospital stay, readmissions, opioid and nonsteroidal anti-inflammatory drug prescriptions, and pain pumps were included in the outcomes analyzed Kirkness et al.[20] The authors found that the mean hospital cost per patient undergoing total knee arthroplasty was significantly lower with LB versus usual care. Since most hand surgery is performed in the outpatient setting, research about potential cost savings for upper-extremity surgery is worthy of future investigation. Cost differential and postoperative pain control differences with the use of LB may be especially relevant for Wide-Awake Local Anesthesia No Tourniquet surgeries where patients have no benefit of a long-acting regional anesthesia. However, to guard against potential toxicity the surgeon would need to avoid exceeding the recommended dose of LB.

To minimize variability in patient selection, procedure performed, surgical technique, LB dose, anesthetic technique, or postoperative pain medication prescriptions, this study was designed with a single variable: LB wound site injection, in a standardized dose and technique. Choosing one type of elective surgical procedure allows a homogeneous cohort. A single surgeon using a standard LB dose and injection protocol helps avoid any inconsistencies with dose or injection location. The standardization of these parameters is a strength of our study but may limit the ability to generalize the results to other procedures or settings. Other limitations of our study include the small sample size and the inclusion of only CMC arthroplasties.

Although we found a statistically significant reduction in total opioid use during the first 5 days after surgery in the patients who received the intraoperative LB injection. Whether this reduction in opioid use is sufficient to decrease addiction risk or other untoward consequences remains unknown. With the finding of a significant decrease in opioid use, the authors now routinely use LB injection during thumb CMC arthroplasty.

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REFERENCES

1. Gauger EM, Gauger EJ, Desai MJ, Lee DH. Opioid use after upper extremity surgery. *J Hand Surg Am*. 2018;43(5):470–479.
2. Waljee JF, Zhong L, Hou H, Sears E, Brummett C, Chung KC. The use of opioid analgesics following common upper extremity surgical procedures: a national, population-based study. *Plast Reconstr Surg*. 2016;137(2):355e–364e.
3. Rodgers J, Cunningham K, Fitzgerald K, Finnerty E. Opioid consumption following outpatient upper extremity surgery. *J Hand Surg Am*. 2012;37(4):645–650.
4. Johnson SP, Chung KC, Zhong L, et al. Risk of prolonged opioid use among opioid-naïve patients following common hand surgery procedures. *J Hand Surg Am*. 2016;41(10):947–957.
5. Kim N, Matzon JL, Abboudi J, et al. A prospective evaluation of opioid utilization after upper-extremity surgical procedures: identifying consumption patterns and determining prescribing guidelines. *J Bone Joint Surg Am*. 2016;98(20):e89.
6. Kelley BP, Shauver MJ, Chung KC. Management of acute postoperative pain in hand surgery: a systematic review. *J Hand Surg Am*. 2015 Aug;40(8):1610–1619. 1619.e1.
7. de Araújo DR, Ribeiro LNM, de Paula E. Lipid-based carriers for the delivery of local anesthetics. *Expert Opin Drug Deliv*. 2019;16(7):701–714.
8. Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ. Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: results of a randomized controlled trial. *J Arthroplasty*. 2018;33(1):90–96.
9. Alter TH, Liss FE, Ilyas AM. A prospective randomized study comparing bupivacaine hydrochloride versus bupivacaine liposome for pain management after distal radius fracture repair surgery. *J Hand Surg Am*. 2017;42(12):1003–1008.
10. Ketonis C, Kim N, Liss F, et al. Wide-awake trigger finger release surgery: prospective comparison of Lidocaine, Marcaine, and Exparel. *Hand (N Y)*. 2016;11(2):177–183.
11. Dale EL, Kluemper CT, Cowart SJ, et al. Bupivacaine extended-release liposomal injection versus bupivacaine HCl for early postoperative pain control following wrist operations: a prospective, randomized control trial. *J Hand Surg Am*. 2020;45(6):550.e1–550.e8.

12. Thompson KM, Smith RA, Brolin TJ, Azar FM, Throckmorton TW. Liposomal bupivacaine mixture has similar pain relief and significantly fewer complications at less cost compared with indwelling interscalene catheter in total elbow arthroplasty. *J Shoulder Elbow Surg*. 2018;27(12):2257–2261.
13. Dysart S, Snyder MA, Mont MA. A randomized, multicenter, double-blind study of local infiltration analgesia with liposomal bupivacaine for postsurgical pain following total knee arthroplasty: rationale and design of the PILLAR trial. *Surg Technol Int*. 2016;30:261–267.
14. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *J Pain Res*. 2012;5:107–116.
15. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain*. 2014;30(2):102–110.
16. Vyas KS, Rajendran S, Morrison SD, et al. Systematic review of liposomal bupivacaine (Exparel) for postoperative analgesia. *Plast Reconstr Surg*. 2016;138(4):748e–756e.
17. Portillo J, Kamar N, Melibary S, Quevedo E, Bergese S. Safety of liposome extended-release bupivacaine for postoperative pain control. *Front Pharmacol*. 2014;5:90.
18. Baxter R, Bramlett K, Onel E, Daniels S. Impact of local administration of liposome bupivacaine for postsurgical analgesia on wound healing: a review of data from ten prospective, controlled clinical studies. *Clin Ther*. 2013;35(3):312–320.e5.
19. Gadsden J, Long WJ. Time to analgesia onset and pharmacokinetics after separate and combined administration of liposome bupivacaine and bupivacaine HCl: considerations for clinicians. *Open Orthop J*. 2016;10:94–104.
20. Kirkness CS, Asche CV, Ren J, Kim M, Rainville EC. Cost-benefit evaluation of liposomal bupivacaine in the management of patients undergoing total knee arthroplasty. *Am J Health Syst Pharm*. 2016;73(9):e247–e254.