Brachial Plexus Block with Liposomal Bupivacaine for Shoulder Surgery Improves Analgesia and Reduces Opioid Consumption: Results from a Multicenter, Randomized, Double-Blind, Controlled Trial

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Abstract

Objective. The utility of single-injection and continuous peripheral nerve blocks is limited by short duration of analgesia and catheter-related complications, respectively. This double-blind, multicenter trial evaluated the efficacy, safety, and pharmacokinetics of single-injection, ultrasound-guided brachial plexus block (BPB) with liposomal bupivacaine (LB) added to a standardized pain management protocol for shoulder surgery. **Methods.** Adults undergoing total shoulder arthroplasty or rotator cuff repair were randomized to receive LB 133 mg, LB 266 mg (pharmacokinetic and safety analyses only), or placebo, added to a standardized analgesia protocol. The primary end point was area under the curve (AUC) of visual analog scale pain intensity scores through 48 hours postsurgery. Secondary end points were total opioid consumption, percentage of opioid-free patients, and time to first opioid rescue through 48 hours. Pharmacokinetic samples were collected through 120 hours and on days 7 and 10. Adverse events were documented. **Results.** One hundred fifty-five patients received treatment (LB 133 mg, N = 69; LB 266 mg, N = 15; placebo, N = 71). BPB with LB 133 mg was associated with significantly improved AUC of pain scores (least squares mean [SE] = 136.4 [12.09] vs 254.1 [11.77], $P < 0.0001$), opioid consumption (least squares mean [SE] = 12.0 [2.27] vs 54.3 [10.05] mg, $P < 0.0001$), median time to opioid rescue (4.2 vs 0.6 h, $P < 0.0001$), and percentage of opioid-free patients (treatment difference = 0.166, 95% confidence interval = 0.032–0.200, $P = 0.008$) through 48 hours vs placebo. Adverse event incidence was comparable between groups. **Conclusions.** Single-injection BPB with LB 133 mg provided analgesia through 48 hours postsurgery with reduced opioid use compared with placebo after shoulder surgery.

Introduction

Effective postsurgical pain relief facilitates rehabilitation after shoulder surgery [1] and is associated with reduced postoperative adhesions, capsule retractions, and intraarticular deposits of fibrous tissue [1] that contribute to shoulder stiffness, a common complication of shoulder repair [2]. Opioid analgesics are routinely prescribed after orthopedic surgery [3], and orthopedic patients have some of the highest opioid prescription rates in the United States [4]. Upper arm and shoulder surgeries are associated with the highest opioid consumption among upper-extremity procedures [5]. Opioid-related adverse effects are associated with longer hospital stays, higher readmission rates, and increased cost [6]. Moreover, reports indicate that approximately 6% of patients continue to use opioids long term after elective procedures [7].

To optimize analgesia after shoulder surgery, current practice favors multimodal approaches [8], including regional anesthesia using interscalene brachial plexus block (BPB) [1]. However, the effectiveness of single-injection BPB is limited by the short analgesia duration of traditional immediate-acting local anesthetics, breakthrough pain, and continued need for postoperative opioids [9]. When combined with immediate-acting local anesthetics, adjuvants such as dexamethasone can prolong BPB [10] by a mean of six to eight hours, resulting in a mean analgesia duration ranging from approximately three to 31 hours across studies [11]. Continuous BPB with infusion pumps and interscalene catheters offers more prolonged analgesia but is time and resource intensive, delivers high total doses of local anesthetics [12], is associated with risk of complications such as device failure and infection, and is subject to user error [9, 12]. A 5% displacement rate has been reported for interscalene catheters within six hours postinsertion, and risk of displacement increases with duration of use [13]. Thus, clinical need remains for longer-acting, simple-to-administer local anesthetics that can provide prolonged analgesia after major surgeries such as total shoulder arthroplasty (TSA) and rotator cuff repair (RCR).

Liposomal bupivacaine (LB; EXPAREL, bupivacaine liposome injectable suspension; Pacira BioSciences, Inc., Parsippany, NJ, USA) is approved by the US Food and Drug Administration (FDA) for single-dose infiltration into the surgical site and as interscalene BPB to produce postsurgical analgesia [14]. Although results from previous studies have varied, LB has been shown to reduce pain and opioid consumption in the first 72 hours postsurgery in a number of surgical models and studies when used as local infiltration analgesia [15]. Randomized controlled trials (RCTs) comparing local infiltration of LB vs interscalene BPB for shoulder arthroplasty have produced mixed findings [16–18]. Data on LB as a peripheral nerve block (PNB) are limited, but interscalene BPB using LB plus bupivacaine HCl significantly reduced worst pain scores vs BPB with bupivacaine HCl alone the first week after TSA or RCR [19]. Here we report results from a placebo-controlled trial designed to evaluate the efficacy and safety of LB 133 mg and safety of LB 266 mg as single-injection BPB added to a standardized pain management protocol for TSA or RCR, which provided the basis for FDA approval for this indication.

Methods

Study Design

This phase III, multicenter, randomized, double-blind, placebo-controlled study (Clinicaltrials.gov NCT02713 230; registered March 15, 2016) was conducted in support of an FDA submission and designed to meet the standards for analgesic approval (ie, placebo control) and to determine a complete safety profile, including sensorimotor effects. It took place between May 6, 2016, and July 7, 2017, at 16 sites in the United States, Belgium, and Denmark with local institutional review board/independent ethics committee approval. It was performed in accordance with the International Conference on Harmonisation Good Clinical Practice (GCP) or US FDA Title 21 Code of Federal Regulations part 56 and the Declaration of Helsinki. All patients provided written informed consent before participation.

Patients

Patients were aged ≥18 years undergoing primary unilateral TSA or RCR under general anesthesia; RCR required magnetic resonance imaging confirmation of ≥1-cm tear. American Society of Anesthesiologists physical status 1, 2, or 3 and normal preoperative motor (ie, Lovett scale for biceps, wrist, and thumb movement score = 5) and sensory function (ie, sensitivity to cold/pinprick/light touch) were required. Exclusion criteria were concurrent surgical procedure or condition that may have required postoperative analgesics; contraindication to bupivacaine or oxycodone; history of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics; smoking history ≥25 pack-years; body mass index >44 kg/m^2; history of renal impairment, chronic respiratory disease, rheumatoid arthritis, or coagulopathy; history of malignancy within two years; history of substance abuse within one year; current renal or hepatic impairment; uncontrolled psychiatric or neurologic disorder; and chronic neuromuscular deficit affecting the surgical limb.

Treatments

Randomization codes, with a block size of six, were generated by a centralized randomization system that communicated patient randomizations to the study site. Study site was not included as a stratification factor. Patients were initially randomized 1:1:1 to receive LB 133 mg, LB 266 mg, or saline placebo (20 mL total volume each) administered as an ultrasound-guided, single-dose BPB one or more hours preoperatively in addition to a standardized pain management protocol. Based on published results [19] showing effectiveness of LB 133 mg against active control, LB 133 mg was chosen as the minimal effective dose to be evaluated. In consideration of costs and time associated with maintaining three treatment arms, an administrative decision was made to amend the protocol to stop randomization to LB 266 mg after collecting adequate safety data and achieving sufficient patient numbers for pharmacokinetics assessment (N = 15) and to continue randomization 1:1 to LB 133 mg or saline placebo. The randomization process was not altered after removal of the LB 266 mg treatment arm. When this arm was removed, it was blocked from randomization. The randomization sequences and codes for the other treatment arms were not changed.

The brachial plexus was visualized using a 13–10-MHz linear transducer placed over the external jugular vein approximately 3 cm cranial to the clavicle until visualization of the C5 and C6 nerve roots was obtained. A blunt-tip block needle was advanced using an "in-plane" approach posterior to anterior toward the superior part of the brachial plexus (C5-C6) at the level of standard approach for interscalene block, and 20 mL of blinded study drug or saline was injected. If spread was inadequate, the needle tip was repositioned; correct tip placement was documented by saving an ultrasound image. Unblinded study personnel uninvolved with postoperative assessments obtained randomization assignments and prepared and administered the study drug; patients and personnel conducting assessments were blinded.

A standardized pain management protocol was implemented for all patients. Preoperative analgesics were limited to oral or intravenous (IV) acetaminophen 1,000 mg every eight hours (maximum, 3,000 mg/d) and low-dose aspirin for cardioprotection. The following were prohibited: long-acting opioids, nonsteroidal anti-inflammatory drugs (NSAIDs; except daily low-dose aspirin), or dexmedetomidine within three days of study drug; any opioid ≤24 hours preoperatively; systemic glucocorticosteroids within one month of enrollment; and initiation of selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, gabapentin, pregabalin, or duloxetine within one month of study drug administration or if used for pain management. Patients taking a stable dose of antidepressant for at least one month before LB administration and using the antidepressant for a purpose other than to control pain were eligible to participate. Intraoperative medication was limited to short-acting opioids (ie, fentanyl, sufentanil, remifentanil); long-acting opioids, acetaminophen, ketorolac, or other NSAIDs were prohibited except for emergency use to treat adverse events (AEs). Admixing with LB and use of other local anesthetics were prohibited intraoperatively. Postsurgically, patients received oral or IV acetaminophen up to 1,000 mg every eight hours, unless contraindicated. Postsurgical pain rescue medication was limited to oxycodone (10 mg every four hours as needed) or, if unable to tolerate oral medication, IV morphine (2.5–5 mg) or hydromorphone (0.5–1 mg). Patient-controlled analgesia was prohibited. All other analgesics were prohibited within 72 hours after study drug; other local anesthetics were prohibited through day 10 postsurgery. Patients were required to remain at the hospital through 72 hours postsurgery.

Efficacy Assessments

Pain intensity scores were assessed using a 10-cm visual analog scale (VAS) on day 0 before PNB/premedication; upon postanesthesia care unit (PACU) arrival, every 15 minutes thereafter, and at PACU discharge; at 6, 12, 24, 36, 48, 60, and 72 hours; and immediately before each rescue medication dose through 72 hours. Date, time, and amount of rescue medication use were recorded through 72 hours. The patient-related outcomes Overall Benefit of Analgesia Score (OBAS; range, 0–28; lower score = greater benefit) and patient satisfaction with overall analgesia (5-point Likert scale) were assessed at 24 and 72 hours and postsurgical day 10. Discharge readiness was evaluated using Modified Postanesthesia Discharge Scoring System (MPADSS) criteria at 12, 24, 36, 48, 60, and 72 hours (or discharge). Unscheduled, pain-related phone calls or office visits were recorded through postsurgical day 10.

Safety Assessments

AEs were documented through postsurgical day 29. Clinical laboratory tests, vital signs, and electrocardiogram were performed at baseline and postsurgery. Neurologic assessment was performed at baseline; PACU arrival; 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and postsurgical days 5 and 10. Patients underwent testing for sensory (cold/pinprick/light touch; shoulder, forearm, fifth/middle fingers, thumb) and motor function (elbow flexion, thumb abduction/adduction/opposition; Lovett scale: 0 = zero; 1 = trace; 2 = poor; 3 = fair; 4 = good; 5 = normal) at baseline; approximately 15, 30, and 45 minutes; PACU discharge; 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours; and postsurgical days 5, 10, and 29, continuing only if prior assessment showed persisting deficit.

Pharmacokinetic Assessments

The three pharmacokinetic sampling schedules all included sampling at baseline (before PNB) and PACU

arrival. Before blinded interim pharmacokinetic analyses, the schedule included additional sampling at 6, 9, 12, 24, 36, 48, 60, 64, 68, 72, 76, 80, 84, 96, and 120 hours (or until discharge). After blinded interim pharmacokinetic analyses, patients were randomly assigned to sampling at 12, 24, 40, 52, and 72 hours or at 24, 36, 48, and 60 hours and discharge.

Venous plasma samples were analyzed by ABS Laboratories Ltd. (Herts, UK) using liquid chromatography tandem mass spectrometry (LC-MS/MS) and multiple reaction monitoring, with bupivacaine-d9 used as an internal standard. For extraction, 50 μL of sample, 20 μL of internal standard working solution, 500 μL of 1.8-M ammonium hydroxide, and 500 μL of methyl tert-butyl ether were added to a 96-well assay plate. After sealing the plate, the samples were mixed for four minutes at 1,400 rpm and then centrifuged for five minutes at 4,000 rpm. A 50-μL aliquot of the supernatant was then transferred to a new sample well and dried under nitrogen at room temperature. After drying, the sample was reconstituted with 500 μL of 0.1% formic acid, vortexed for four minutes at 900 rpm, and centrifuged for five minutes at 4,000 rpm. A 10-μL sample was then analyzed using LC-MS/MS (Applied Biosystems API4000 fitted with TurboIonSpray). The calibration curve for the assay included nine bupivacaine standards (1, 2, 5, 10, 25, 100, 250, 500, 1,000 ng/mL) in blank human plasma; three quality control samples (3, 50, and 800 ng/mL) were used. The lower limit of quantification for the assay was 1 ng/mL. Accuracy ranged from 97.2% to 101.5% for the calibration curve, with the coefficient of variability ranging from 2.0% to 4.7%.

End Points

The primary efficacy end point was area under the curve (AUC) of VAS pain intensity scores through 48 hours postsurgery ($AUC_{0–48}$). Secondary efficacy end points included total postsurgical (oral and IV) opioid consumption (mg IV morphine equivalents) (conversion factors are shown in the Supplementary Data), percentage of opioid-free patients, and time to first opioid rescue through 48 hours. Tertiary efficacy end points included VAS pain intensity scores and percentage of pain-free patients (VAS pain intensity score ≤1.5 without prior rescue medication) at each time point; AUC of pain intensity scores through 12 hours; AUC of pain intensity scores and total opioid consumption through 24 and 72 hours and from 24–48 and 48–72 hours; percentage of opioid-free patients through 24 and 72 hours; sum of pain intensity scores (SPIS) at 12, 24, 48, and 72 hours and from 24–48 and 48–72 hours; OBAS; patient satisfaction with overall analgesia; percentage of discharge-ready patients (meeting MPADSS criteria) at 12, 24, 36, 48, 60, and 72 hours; time to discharge readiness; and number of pain-related unscheduled calls or office visits.

Safety end points included incidence of treatment-emergent AEs (TEAEs [AEs with onset between study drug initiation and day 30]), serious AEs (SAEs), and AEs of special interest (cardiac, neurologic, falls [monitored per FDA guidance as a potential indicator of local anesthetic systemic toxicity]); change from baseline in clinical laboratory assessments, vital signs, and electrocardiogram; and neurologic, sensory, and motor function. Median times to return of sensory function (no deficits) and motor function (score = 5) were calculated.

Pharmacokinetic end points included maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), and apparent terminal elimination half-life ($t_{1/2}$) derived using samples collected before blinded interim pharmacokinetic analyses.

Statistical Analysis

Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., USA). Sample size was calculated based on the AUC of the numeric rating scale at rest pain intensity scores through 48 hours, as reported in a previous PNB study [20]. Assuming a two-sided 0.05 alpha and common SD of 97, 69 patients/arm were needed to detect a 46.6-unit treatment difference in mean AUC of pain intensity scores with approximately 80% power.

Safety analyses included all patients who received the study drug and were based on actual treatment received. Efficacy analyses included all patients who received LB 133 mg or placebo and who underwent the surgery and were based on randomized treatment. Pharmacokinetic analyses included all patients who received LB 133 or 266 mg, provided sufficient samples, and had no significant protocol deviations.

The primary end point was analyzed using analysis of variance (ANOVA) with treatment and site as main effects (alpha = 0.025). Least squares (LS) means were used to adjust for covariates (age, weight, height). Imputation of pain intensity scores was performed to account for missing pain intensity scores and the use of rescue medication. Missing scores before the first nonmissing score were replaced by the median score at the missing time point from other patients receiving the same treatment. Missing scores after the last nonmissing score were replaced using a last-observation-carried-forward approach; those between two nonmissing scores were replaced using linear interpolation. For patients who received rescue medication, windowed worst-observation-carried-forward imputation was applied: all pain intensity scores recorded within the rescue medication window were replaced by the highest score recorded between end of surgery and first rescue medication use or, if not available, the highest recorded score. To determine whether imputation had a meaningful effect on the primary end point, a post hoc analysis was performed using unimputed pain scores.
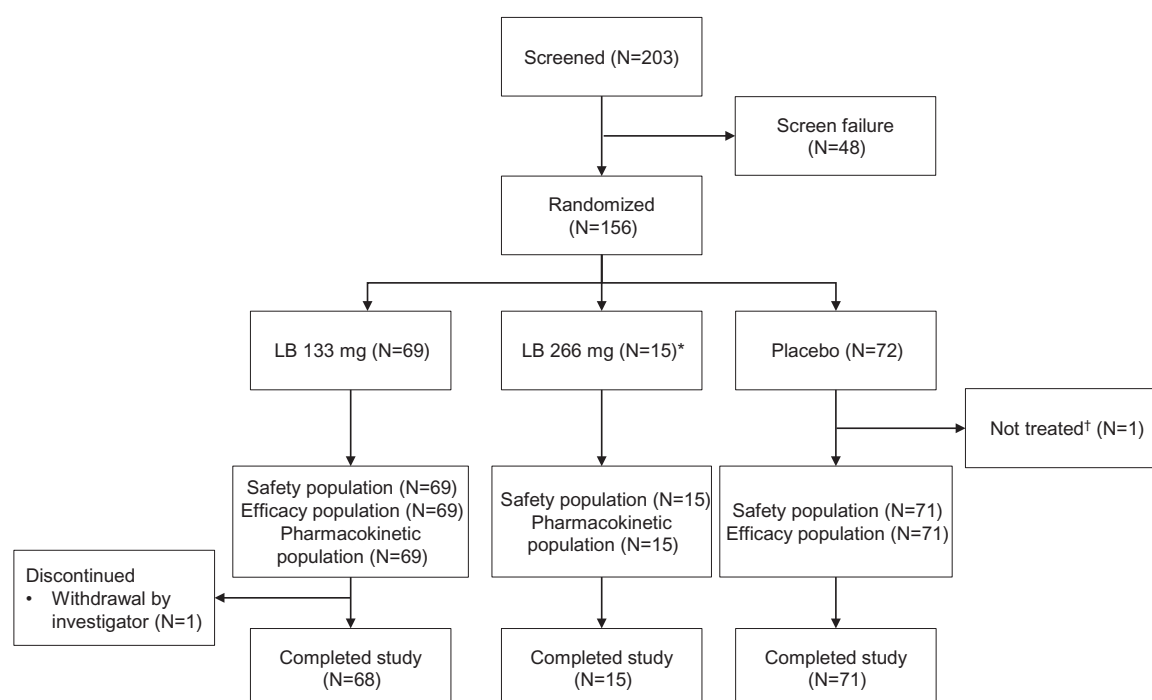
Figure 1. Patient disposition. *An administrative decision was made to amend the protocol to stop randomization to LB 266 mg after achieving sufficient patient numbers for pharmacokinetics assessment (N = 15) and continue randomization 1:1 to LB 133 mg or placebo. All of these patients received the study drug and completed the study; they were included in analyses of pharmacokinetics and safety only. [†]One patient failed screening and was not enrolled but was randomized in error; the patient did not receive the study drug and was not included in the analyses. LB = liposomal bupivacaine.

Secondary end points, for which this study was not powered, were analyzed using a hierarchical, fixed-sequence, stepwise testing approach starting with total postsurgical opioid consumption if the primary end point was significant (alpha = 0.05). Opioid consumption data were not normally distributed; therefore, they were log-transformed before analysis, and LS means (predicted means if data distribution was balanced) were reported instead of arithmetic means (parameter for normally distributed data) or medians. Percentages of opioid-free patients were analyzed using a Cochran-Mantel-Haenszel test stratified by site. Time to first opioid rescue was analyzed using a Kaplan-Meier survival plot. A blinded automatic computer program was used to conduct these evaluations according to the preset rules.

Percentages of pain-free patients were analyzed using normal approximation to the binomial distribution and the Cochran-Mantel-Haenszel test. SPIS was analyzed using ANOVA. Patient satisfaction with overall analgesia and OBAS were analyzed using the Kruskal-Wallis test. Kaplan-Meier estimates and log-rank tests were used for analysis of discharge readiness and post hoc analyses of times to complete return of sensory and motor (score = 5, all assessments) function. Analyses by surgery type were exploratory. Pharmacokinetic parameters were estimated by noncompartmental analysis. Pharmacokinetic and safety parameters and pain-related unscheduled phone calls or office visits were summarized descriptively.

Results

Patients
Of 156 randomized patients, 155 received treatment (LB 133 mg, N = 69; LB 266 mg, N = 15; placebo, N = 71) (Figure 1) , including 112 undergoing RCR and 42 undergoing TSA (one patient's surgery type was unknown). Baseline demographic and clinical characteristics were well balanced (Table 1). Patient disposition by study site is provided in the Supplementary Data.

Efficacy
BPB with LB 133 mg was associated with significantly reduced pain scores through 48 hours vs placebo (LS mean [SE] AUC_{0-48} = 136.4 [12.09] vs 254.1 [11.77], $P < 0.0001$) (Table 2). In the analysis of pain scores without imputation, LS mean AUC_{0-48} remained significantly in favor of BPB with LB (139.2 [11.49] vs 227.3 [11.25], $P < 0.0001$) (Table 2). Per-protocol analysis also confirmed this finding. There was no treatment-by-study site interaction. All three secondary efficacy outcomes significantly favored LB (Table 2). LB was associated with significantly reduced total postsurgical opioid (oral and IV) consumption ($P < 0.0001$) and significantly prolonged median time to first rescue opioid ($P < 0.0001$) through 48 hours vs placebo. LB-treated patients were nine times more likely to be opioid-free through 48 hours (13% vs 1%, risk ratio [RR] = 9.26, 95% confidence interval [CI]

Table 1. Patient demographic and baseline clinical characteristics

Characteristic*	TSA[†]		RCR[†]		Overall[†]	
	LB 133 mg (N = 19)	Placebo (N = 15)	LB 133 mg (N = 50)	Placebo (N = 55)	LB 133 mg (N = 69)	Placebo (N = 71)
Age, y	65.2 (8.60)	64.9 (8.17)	58.9 (9.95)	56.5 (8.96)	60.6 (9.94)	58.5 (9.48)
Women, No. (%)	8 (42.1)	7 (46.7)	17 (34.0)	15 (27.3)	25 (36.2)	23 (32.4)
Right hand dominant, No. (%)	18 (94.7)	13 (86.7)	41 (82.0)	47 (85.5)	59 (85.5)	61 (85.9)
BMI, kg/m^{2‡}	32.1 (4.24)	29.2 (6.05)	30.2 (4.61)	30.3 (5.37)	30.7 (4.56)	30.2 (5.49)
ASA classification, No. (%)						
1	1 (5.3)	3 (20.0)	14 (28.0)	11 (20.0)	15 (21.7)	14 (19.7)
2	11 (57.9)	8 (53.3)	25 (50.0)	28 (50.9)	36 (52.2)	37 (52.1)
3	7 (36.8)	4 (26.7)	11 (22.0)	16 (29.1)	18 (26.1)	20 (28.2)
VAS score, cm	2.3 (2.98)	2.5 (2.82)	2.5 (2.51)	3.1 (2.43)	2.4 (2.62)	2.9 (2.51)
Prior opioid use, No. (%)	5 (26.3)	3 (20.0)	5 (10.0)	7 (12.7)	10 (14.5)	11 (15.5)
Duration of surgery, h	1.9 (0.49)	2.0 (0.66)	0.9 (0.61)	1.0 (0.71)	1.2 (0.71)	1.3 (0.80)
Total incision length, cm§	12.2 (2.46)	12.3 (3.92)	3.7 (3.86)	3.4 (2.56)	5.6 (5.09)	5.2 (4.56)

One placebo-treated patient with missing type of surgery is not included in the breakdown by subgroup.

ASA = American Society of Anesthesiologists; BMI = body mass index; LB = liposomal bupivacaine; RCR = rotator cuff repair; TSA = total shoulder arthroplasty; VAS = visual analog scale.

*Mean (SD) unless otherwise specified.

[†]LB 266 mg: TSA, N = 8; RCR, N = 7; overall, N = 15.

[‡]TSA: N = 18 LB, N = 15 placebo; overall: N = 68 LB, N = 71 placebo.

[§]TSA: N = 12 LB, N = 10 placebo; RCR: N = 40 LB, N = 44 placebo; overall: N = 52 LB, N = 55 placebo.

= 1.20–71.17). Results for secondary end points were similar across sites.

VAS pain intensity scores were significantly lower with LB vs placebo at each time point (all $P < 0.05$) (Figure 2) and at each interval assessed over 72 hours postsurgery (all $P \leq 0.01$) (Table 2). In patients who received LB, total postsurgical opioid consumption from 0–24, 24–48, 48–72, and 0–72 hours was significantly reduced by 65% to 86% ($P \leq 0.01$) (Figure 3). LB-treated patients were significantly more likely to be opioid-free than placebo-treated patients through 24 hours (23.2% vs 1.4%, RR = 16.5, 95% CI = 2.2–120.8), with 5.8% remaining opioid-free through 72 hours (RR = 4.1, 95% CI = 0.5–35.9) (Table 2).

Significantly more patients were pain-free postsurgery with LB 133 mg vs placebo, including in the PACU and at each time point up to 48 hours (all $P < 0.05$); differences beyond 48 hours did not reach significance (Figure 4). SPIS scores were significantly lower with LB at each interval assessed over 72 hours (all $P < 0.01$) (Figure 5). OBAS total scores indicated greater analgesia with LB at 24 hours ($P < 0.0001$), but differences did not reach significance at 72 hours. OBAS total score on day 10 was significantly improved with LB vs placebo ($P = 0.005$) (Table 2).

Patient satisfaction with overall analgesia was significantly higher with LB 133 mg vs placebo at each time point (all $P < 0.01$) (Table 2), although modest in terms of clinical significance. A significantly greater proportion of patients were discharge ready as early as 12 hours with LB vs placebo ($P = 0.0187$) (Figure 6); the difference in time to discharge readiness was not statistically significant. At 48 hours, time to discharge readiness was significantly shorter with LB vs placebo (median = 10.8 hours, 95% CI = 10.03–19.72 hours, vs median = 22.4 hours, 95% CI = 19.83–32.85 hours, $P < 0.01$). There were no pain-related unscheduled phone calls or office visits postdischarge.

Safety

The proportion of patients with one or more TEAEs was similar between groups (Table 3); most TEAEs were mild or moderate in severity. Nausea was the most commonly reported AE, followed by constipation (Table 3). Three TEAEs (LB 133 mg) were considered (by the investigator) to be probably related to study drug (hypoesthesia [2]; atelectasis [1]) and 15 to be possibly related (LB 133 mg: dysgeusia [5], headache [4]; nausea, hypoesthesia, injection site pain, dyspnea, ST segment elevation [1 each]; LB 266 mg: sensory loss [1]). Four patients experienced an SAE (LB 266 mg, 1 [pancreatitis]; LB 133 mg, 2 [pseudogout flare, pneumonia]; placebo, 1 [*Clostridium difficile* colitis]). All SAEs resolved and were considered unrelated to study drug by the investigator. One patient (placebo) had a TEAE of fall. No desaturation or increased oxygen requirements were reported as AEs. No signs of respiratory distress were observed in the LB 266 mg group. No clinically significant between-group differences in laboratory values, vital signs, or electrocardiogram were observed.

Neurologic, Sensory, and Motor Function

Neurologic tests were normal in most patients; the proportions (LB 133 mg/placebo) with a neurologic test abnormality at any time point were subject oriented, 0/0;

Table 2. Efficacy end points

End Point	LB 133 mg (N = 69)	Placebo (N = 71)	Difference (95% CI) P Value
Primary			
LS mean (SE) AUC of VAS pain intensity scores through 48 h postsurgery	136.4 (12.09)	254.1 (11.77)	−117.7 (−150.90 to −84.48) <0.0001
Unadjusted mean	134.2 (98.05)	255.3 (105.03)	
Secondary			
LS geometric mean (SE) postsurgical opioid consumption 0–48 h (IV morphine equivalents), mg	12.0 (2.27)	54.3 (10.05)	0.220 (0.131 to 0.371)* <0.0001
Opioid-free patients through 48 h, No. (%)	9 (13.0)	1 (1.4)	0.116 (0.032 to 0.200) 0.008
Median (95% CI) time to first opioid rescue through 48 h, h	4.2 (1.52 to 8.50)	0.6 (0.48 to 0.68)	<0.0001
Tertiary			
LS mean (SE) AUC of VAS pain intensity scores			
0–12 h	26.1 (2.70)	55.3 (2.64)	−29.2 (−36.58 to −21.75) <0.0001
0–24 h	62.3 (5.86)	128.0 (5.72)	−65.6 (−81.75 to −49.53) <0.0001
0–72 h	217.7 (18.96)	363.1 (18.48)	−145.4 (−197.52 to −93.26) <0.0001
24–48 h	73.9 (7.61)	127.5 (7.39)	−53.6 (−74.47 to −32.69) <0.0001
48–72 h	82.7 (8.48)	112.2 (8.28)	−29.5 (−52.83 to −6.15) 0.01
Opioid-free patients, No. (%)			
0–24 h	16 (23.2)	1 (1.4)	22% (11.5% to 32.1%) <0.0001
0–72 h	4 (5.8)	1 (1.4)	4% (−1.8% to 10.5%) 0.16
Mean (SD) OBAS			
24 h[†]	3.5 (3.26)	5.3 (3.07)	<0.0001
72 h[‡]	3.2 (2.68)	4.2 (3.19)	0.056
10 d[§]	1.6 (2.09)	2.8 (2.57)	0.005
Mean (SD) satisfaction with overall analgesia			
24 h[¶]	4.4 (0.81)	3.7 (1.32)	0.002
72 h[‖]	4.5 (0.89)	4.1 (1.09)	0.003
10 d[‖‖]	4.5 (0.95)	4.0 (1.15)	<0.001

AUC = area under the curve; IV = intravenous; LB = liposomal bupivacaine; LS = least squares; OBAS = Overall Benefit of Analgesia Score; VAS = visual analog scale.

*LS treatment ratio (95% CI).
[†]N = 68 LB, N = 69 placebo.
[‡]N = 68 LB.
[§]N = 64 LB, N = 68 placebo.
[¶]N = 68 LB, N = 70 placebo.
[‖]N = 67 LB, N = 71 placebo.
[‖‖]N = 65 LB, N = 69 placebo.

numb lips, tongue, or mouth, 4.3%/0; metallic taste, 8.7%/4.2%; hearing problems, 0/1.4%; vision problems, 0/1.4%; and muscle twitching, 8.7%/12.7%. Most patients treated with LB 133 or 266 mg had transient sensory and motor loss (Figure 7) in the blocked extremity. Median times to loss of sensation with LB 133 and 266 mg were 42 and 18 minutes, respectively; median times to return were 36 and 82 hours, respectively. Time to complete motor function loss significantly differed between LB 133 mg and placebo presurgery (*P* < 0.001) and was not reached for LB 266 mg presurgery; median

time to return for LB 133 and 266 mg was 24 and 49 hours, respectively. Small proportions of patients receiving LB 133 mg had complete motor block (Lovett score = 0) at preoperative (15 min, 3%; 30 min, 1%; 45 min, 3%) or postoperative assessments (PACU, 1%; 6 h, 7%; 9 h, 7%; 12 h, 3%; 18 h, 3%), none persisting beyond 18 hours postsurgery. There were no obvious outliers for sensorimotor return; however, there was a high ratio of censored data due to loss to follow-up postdischarge. Log-rank tests comparing LB 133 mg and placebo showed a significant difference in time to complete
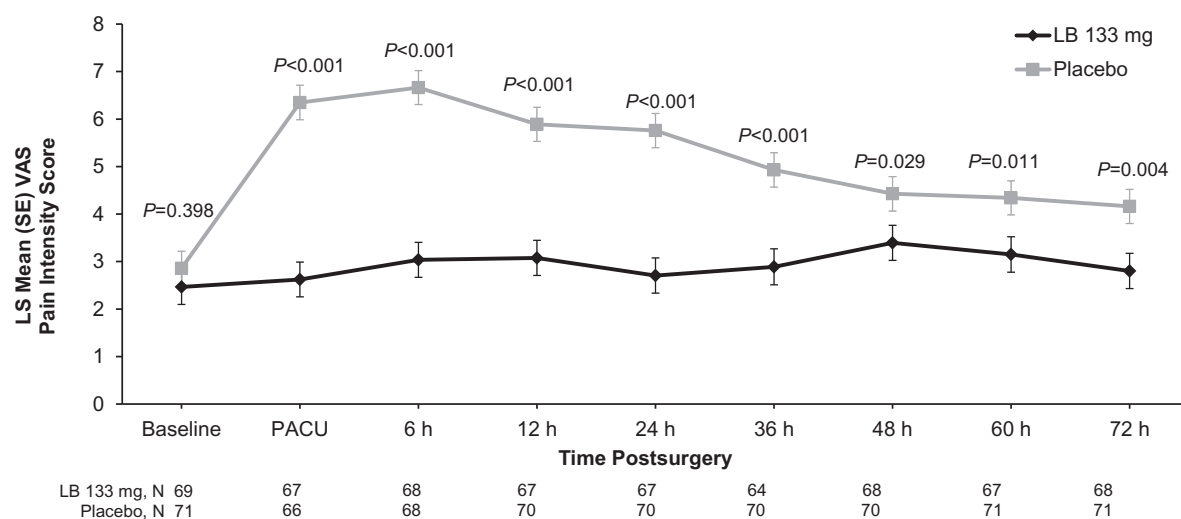
Figure 2. LS mean VAS pain intensity scores through 72 hours. LB = liposomal bupivacaine; LS = least squares; VAS = visual analog scale.
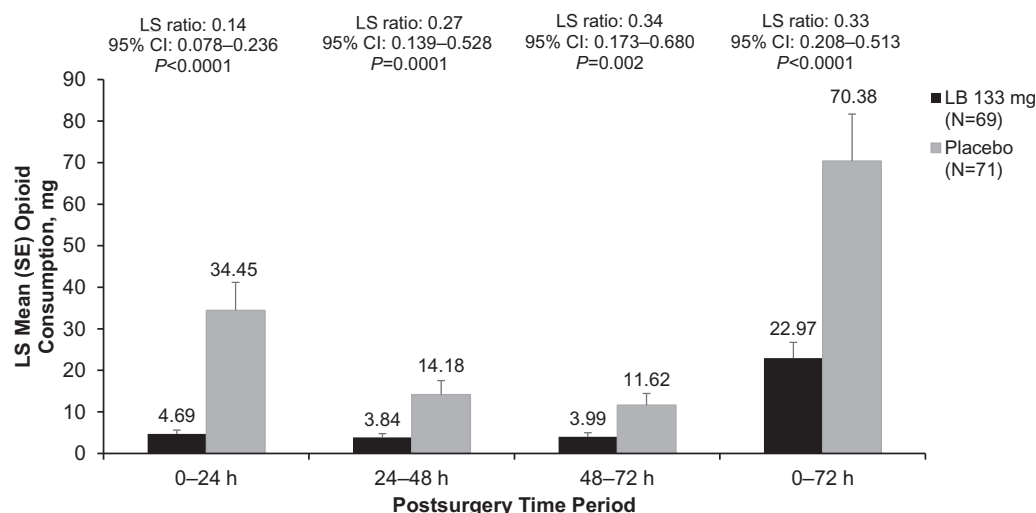

Figure 3. Postsurgical opioid consumption (IV morphine equivalents, mg) over time. IV = intravenous; LB = liposomal bupivacaine; LS = least squares.

sensory return ($P < 0.0001$) but comparable time to complete motor return ($P = 0.6158$).

Pharmacokinetic Analysis

Plasma bupivacaine pharmacokinetic profiles with LB 133 mg included an early peak of 115 ng/mL at six hours and an absolute C_{max} of 209 ng/mL at 48 hours (Figure 8). LB 266 mg showed a similar profile.

Discussion

Addition of single-injection BPB with LB 133 mg to a standardized pain management protocol for shoulder surgery resulted in significant pain reductions, with pain intensity remaining close to preoperative levels through 72 hours vs the standardized protocol alone. In consideration of the costs and time constraints associated with

maintaining the three treatment arms, an administrative decision was made to terminate the LB 266 mg arm after achieving a sufficient number of patients for pharmacokinetic assessments (N = 15) and obtaining sufficient safety data for the 266-mg dose. LB 133 mg was also associated with statistically significant improvements for the secondary end points, percentage of pain-free patients and SPIS and OBAS total scores. LB-treated patients had 46% lower AUC_{0-48}, 78% less opioid consumption, and were nine times more likely to be opioid-free at 0–48 hours. These findings led to FDA approval of LB for interscalene BPB to produce postsurgical analgesia [14].

With plain bupivacaine HCl single-injection PNBs, many patients need opioid rescue because the duration of analgesia (~12 hours) is shorter than the postsurgical pain duration, which also exceeds the duration of analgesia with plain bupivacaine HCl single-injection PNB with adjuvant dexamethasone (~22 hours) [11]. The present
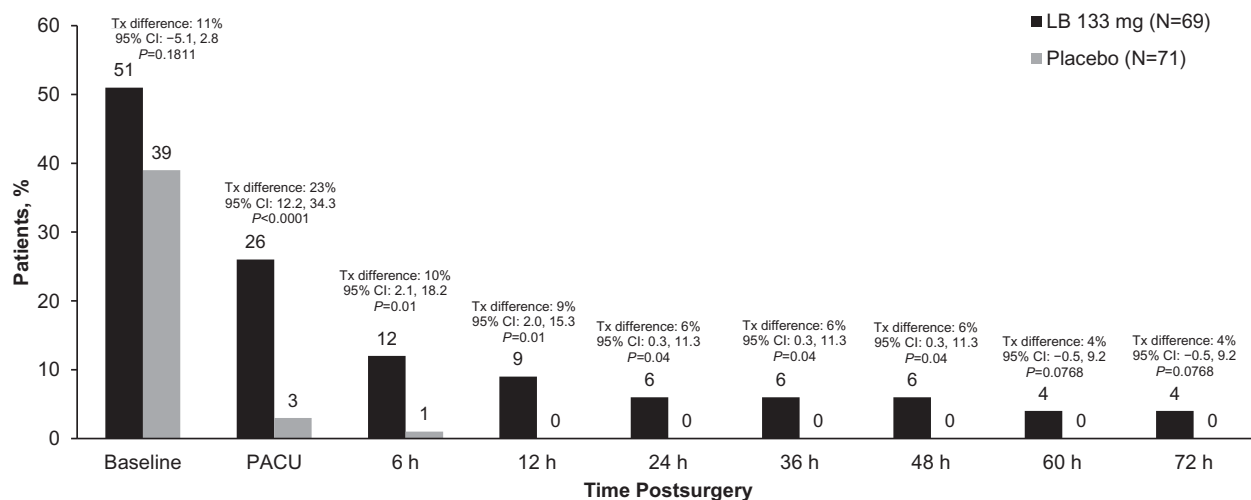
Figure 4. Percentage of pain-free patients over time. LB = liposomal bupivacaine; PACU = postanesthesia care unit; Tx = treatment.
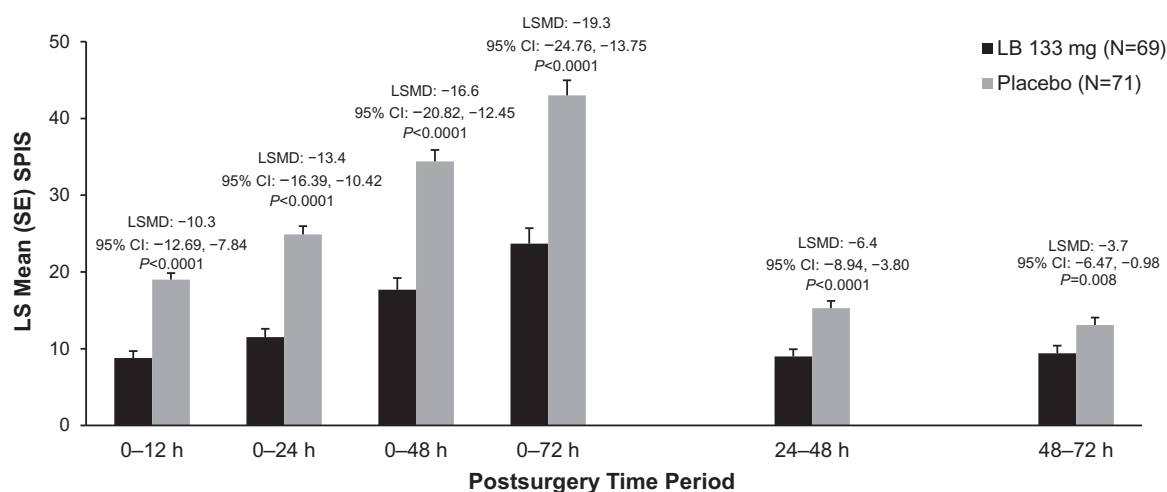
Figure 5. LS mean SPIS scores over time. LB = liposomal bupivacaine; LS = least squares; LSMD = LS mean difference; SPIS = sum of pain intensity scores.

data support the safety and efficacy of LB 133 mg for long-acting PNB in patients receiving opioids for postsurgical pain, showing improvement in pain scores as well as patient-reported quality of analgesia and satisfaction. Importantly, we observed durable improvements in postsurgical opioid consumption and proportion of opioid-free patients, demonstrating that this approach is consistent with goals to improve pain management with reduced opioid reliance over an extended postsurgical time frame. Preinduction sensorimotor tests and significant reduction in VAS pain scores in the PACU suggest that achieving analgesia was not delayed with LB. The significant improvement in OBAS total score on day 10 in the LB 133 mg group suggests maintenance of analgesia after 72 hours, and no breakthrough pain was observed in LB-treated patients. LB was associated with significantly improved discharge readiness vs placebo; overall discharge readiness times were consistent with literature-reported lengths of stay after TSA (one to three days) [18, 21].

LB single-injection BPB was well tolerated with no unexpected safety concerns. Although this study did not incorporate objective measures of phrenic nerve block (eg, ultrasound assessment of diaphragm movement, pre- vs postinjection chest x-ray), which is a study limitation, there was no clinically manifested respiratory distress. Standardized early motor assessment was not feasible because of postsurgical sling use; however, sensorimotor testing showed that most patients in both treatment groups had transient sensorimotor reduction in the blocked extremity, which normalized at study conclusion. Though sensory reduction was more probable with LB 133 mg, it was also reported in placebo-treated patients, which may reflect perceived numbness or weakness related to the use of cryocuffs/slings or pain-related functional limitation, absent actual sensory deficits.
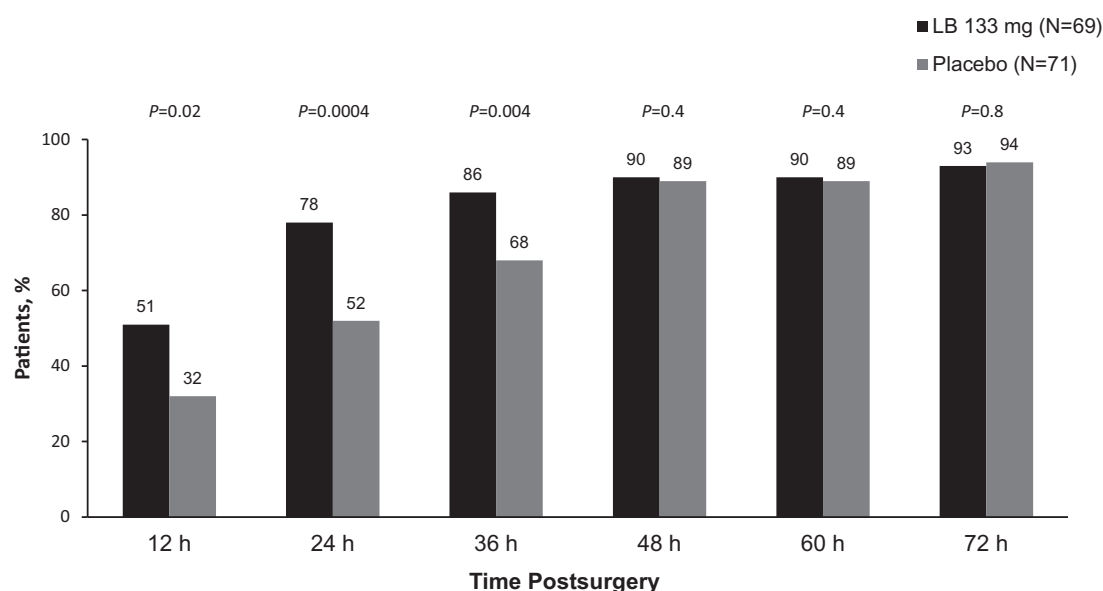
■ LB 133 mg (N=69)
■ Placebo (N=71)

| | *P*=0.02 | *P*=0.0004 | *P*=0.004 | *P*=0.4 | *P*=0.4 | *P*=0.8 |

Figure 6. Proportions of discharge-ready patients over time. LB = liposomal bupivacaine.

Table 3. Summary of treatment-emergent adverse events*

Adverse Event, No. (%)	LB 133 mg (N = 69)	LB 266 mg (N = 15)	Placebo (N = 71)
Patients with ≥1 TEAE	55 (79.7)	11 (73.3)	55 (77.5)
TEAEs occurring in ≥5% of patients in any treatment group			
Nausea	17 (24.6)	3 (20.0)	26 (36.6)
Headache	7 (10.1)	1 (6.7)	3 (4.2)
Constipation	6 (8.7)	2 (13.3)	9 (12.7)
Dysgeusia	6 (8.7)	0	3 (4.2)
Pyrexia	6 (8.7)	1 (6.7)	3 (4.2)
Hypoesthesia	6 (8.7)	0	1 (1.4)
Muscle twitching	5 (7.2)	2 (13.3)	8 (11.3)
Vomiting	4 (5.8)	1 (6.7)	7 (9.9)
Pruritus	3 (4.3)	1 (6.7)	11 (15.5)
Dizziness	2 (2.9)	1 (6.7)	9 (12.7)
Hypertension	2 (2.9)	3 (20.0)	6 (8.5)
Insomnia	2 (2.9)	1 (6.7)	0
Sensory loss	2 (2.9)	1 (6.7)	0
Hypotension	1 (1.4)	1 (6.7)	2 (2.8)
Anxiety	1 (1.4)	1 (6.7)	0
Tachycardia	1 (1.4)	1 (6.7)	0
Dyspepsia	1 (1.4)	0	4 (5.6)
Paresthesia	1 (1.4)	1 (6.7)	1 (1.4)
Abdominal pain	0	1 (6.7)	0
Rash	0	1 (6.7)	1 (1.4)
Patients with ≥1 TEAE of special interest	9 (13.0)	3 (20.0)	9 (12.7)
Cardiac disorders	1 (1.4)	1 (6.7)	1 (1.4)
Tachycardia	1 (1.4)	1 (6.7)	0
Sinus tachycardia	0	0	1 (1.4)
Nervous system disorders	5 (7.2)	1 (6.7)	4 (5.6)
Dysgeusia	4 (5.8)	0	2 (2.8)
Paresthesia	1 (1.4)	0	1 (1.4)
Dizziness	0	1 (6.7)	0
Motor dysfunction	0	0	1 (1.4)
Musculoskeletal and connective tissue disorders	3 (4.3)	1 (6.7)	2 (2.8)
Muscle twitching	3 (4.3)	1 (6.7)	2 (2.8)
Ear and labyrinth disorders	0	0	1 (1.4)
Tinnitus	0	0	1 (1.4)
Eye disorders	0	0	1 (1.4)
Visual impairment	0	0	1 (1.4)

LB = liposomal bupivacaine; TEAE = treatment-emergent adverse event.

*A TEAE was defined as an adverse event with onset between the start of study treatment and day 30.
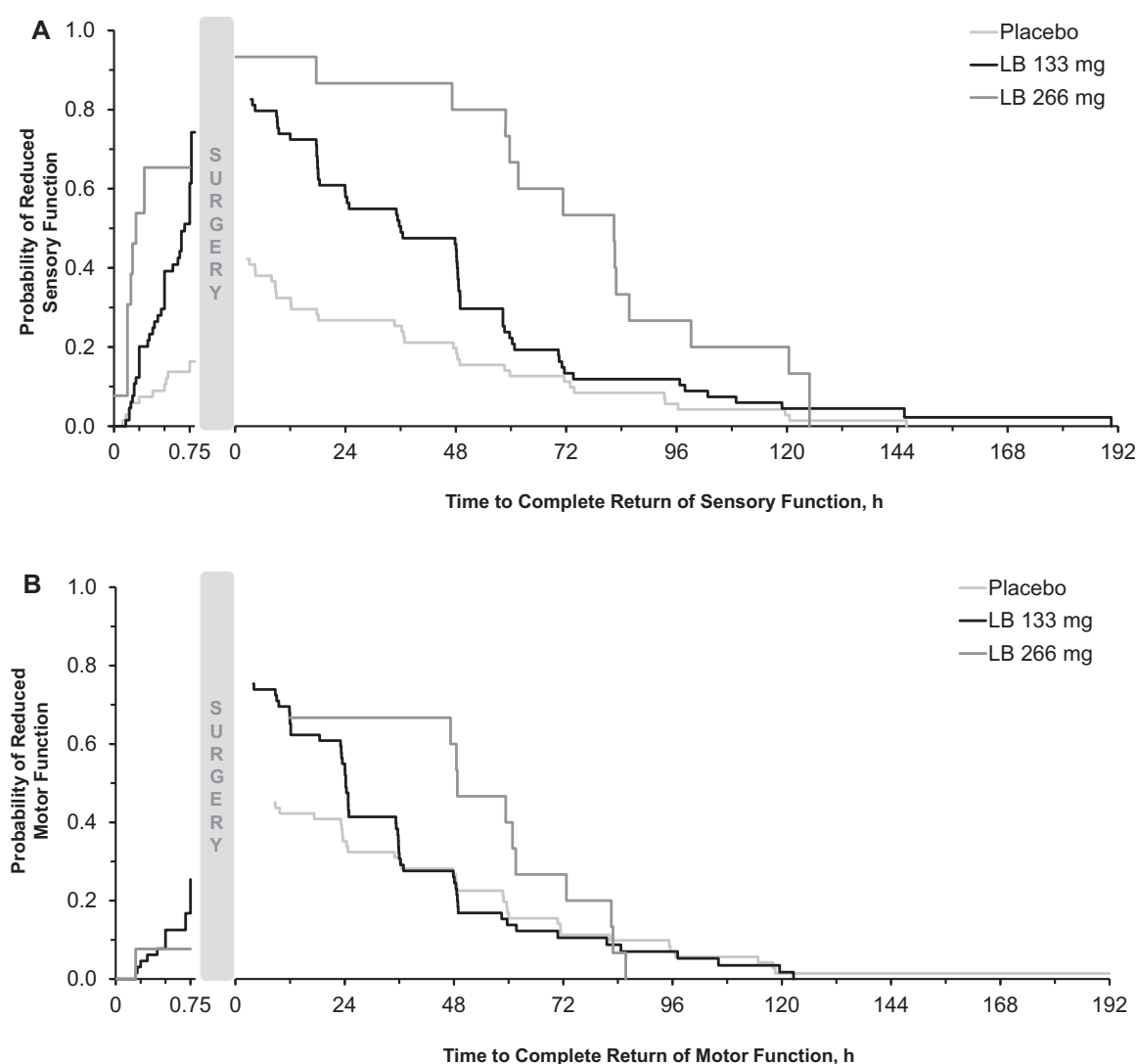
Figure 7. Kaplan-Meier survival plots for return of (A) sensory and (B) motor function (safety analysis set). Sensory function was assessed as the presence/absence of cold, pinprick, and light touch sensations in the distal part of innervated dermatomes (musculocutaneous, median, ulnar, radial, and axillary). Motor function was assessed using elbow flexion and thumb abduction, adduction, and opposition (assessed using the Lovett scale: 0 = zero; 1 = trace; 2 = poor; 3 = fair; 4 = good; 5 = normal); complete return of motor function was defined as a Lovett score of 5 for all elbow and thumb movements. LB = liposomal bupivacaine.

However, the possibility that variability in examination techniques by investigators contributed to reported sensorimotor block cannot be ruled out. Median durations of sensory and motor block (36 and 24 hours, respectively) with LB, though not indicative of analgesia, were longer than mean durations reported in previous studies of BPB with bupivacaine HCl (approximately 4 and 3.5 hours) [22] or bupivacaine plus dexamethasone (approximately 19 and 20 hours) [23]. Median times to block onset with LB (42 minutes to sensory loss with 133 mg LB) were also longer compared with mean times previously reported with bupivacaine HCl (13 and 16 minutes, respectively) [22] or bupivacaine plus dexamethasone (10–16 minutes) [23]. However, comparisons across studies should be made with caution.

Pharmacokinetic findings showed no association with possible treatment-related AEs. Plasma bupivacaine concentrations peaked at approximately 48 hours postinjection, consistent with slow local bupivacaine release. Mean peak concentration for LB 133 and 266 mg (209 and 461 ng/mL, respectively) remained well below expected thresholds for cardiotoxicity and neurotoxicity (2,000–4,000 ng/mL), supporting the safety of both doses [24, 25].

Although a limitation of the study, the use of a placebo comparator, which consisted of BPB with saline added to a standardized pain management protocol, met FDA requirements for this registration trial and facilitated robust safety evaluation, including effects on sensorimotor function. The statistical analysis plan and raw
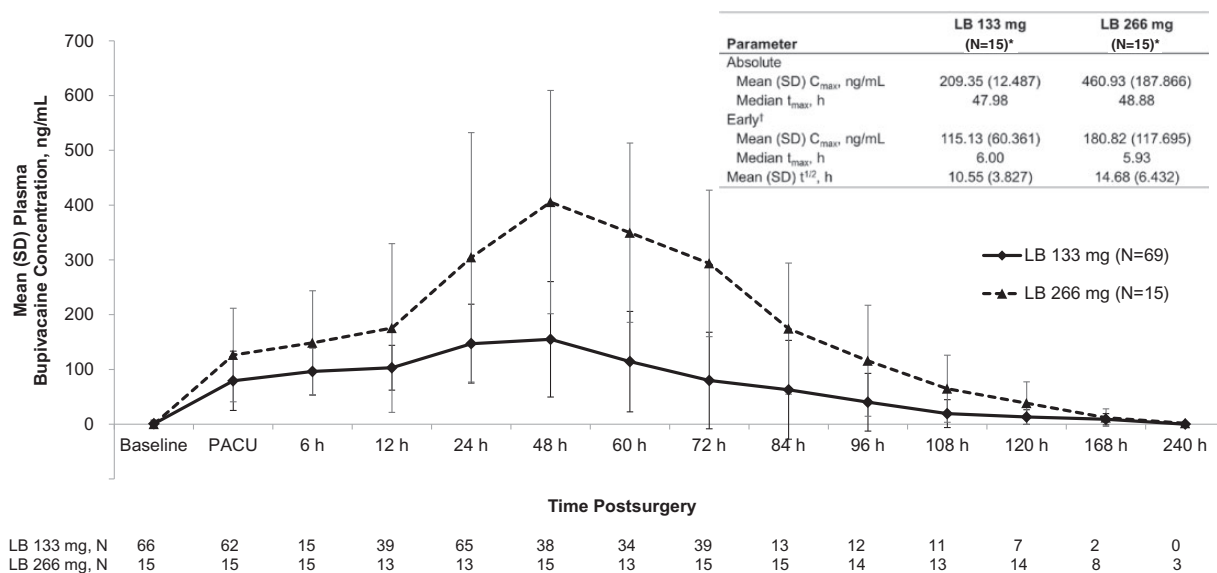
Inset table:

Parameter	LB 133 mg (N=15)*	LB 266 mg (N=15)*
Absolute		
Mean (SD) C_{max}, ng/mL	209.35 (12.487)	460.93 (187.866)
Median t_{max}, h	47.98	48.88
Early[†]		
Mean (SD) C_{max}, ng/mL	115.13 (60.361)	180.82 (117.695)
Median t_{max}, h	6.00	5.93
Mean (SD) $t^{1/2}$, h	10.55 (3.827)	14.68 (6.432)

	Baseline	PACU	6 h	12 h	24 h	48 h	60 h	72 h	84 h	96 h	108 h	120 h	168 h	240 h
LB 133 mg, N	66	62	15	39	65	38	34	39	13	12	11	7	2	0
LB 266 mg, N	15	15	15	13	13	15	13	15	15	14	13	14	8	3

Figure 8. Mean plasma bupivacaine concentration-time profiles and pharmacokinetic parameters for LB 133 mg and LB 266 mg. Figure plots mean values in the pharmacokinetic population (LB 133 mg, N = 69; LB 266 mg, N = 15); inset summarizes bupivacaine pharmacokinetic parameters for patients who underwent pharmacokinetic sampling before the blinded interim pharmacokinetic analysis (LB 133 mg, N = 15; LB 266 mg, N = 15). *Includes only those patients who provided a full pharmacokinetic profile of 17 samples (before the blinded interim pharmacokinetic analysis was performed). [†]Early indicates through two hours. C_{max} = maximum observed plasma concentration; LB = liposomal bupivacaine; PACU = postanesthesia care unit; t_{max} = time to C_{max}; $t_{1/2}$ = apparent terminal elimination half-life.

data were vetted by the FDA as part of the drug approval process for LB when administered as a BPB. The research team maintained GCP standards by implementing a vigorous informed consent process to address alternatives and risks and benefits associated with receiving placebo and a standard-of-care postoperative analgesia plan primarily incorporating opioids. Although treatment guidelines recommend multimodal analgesia, including regional analgesia with local anesthetics [8], PNBs are not universally used for TSA [26, 27], and opioids are still the standard of care in many hospitals [8].

A previous RCT comparing single-injection BPB using LB 133 mg plus bupivacaine HCl vs bupivacaine HCl alone for shoulder surgery demonstrated improvement with LB in worst pain scores and OBAS total scores throughout the first week postsurgery [19]. Those improvements were not associated with reduced opioid consumption, possibly due to uncontrolled opioid-prescribing practices, small sample size, and unreliable postdischarge opioid assessments, as patients were discharged on postsurgical day 1. Consistent with the current study, the addition of LB did not increase risk for complications compared with interscalene BPB with bupivacaine HCl [19]. The current findings are also consistent with a pooled analysis of six studies using LB for ankle, femoral, or intercostal nerve blocks, showing comparable overall TEAE incidence in the LB and placebo groups, with no treatment-related SAEs [28]. Future trials should compare the effectiveness of BPB with LB vs single-injection or continuous BPB with bupivacaine HCl or other local anesthetics and assess long-term patient-related and health economic outcomes. Admixing with bupivacaine HCl may provide additional analgesia during early recovery and warrants further investigation.

Limitations

The use of a placebo comparator is a limitation of the study as we did not compare outcomes of LB with plain bupivacaine HCl when used for BPB. Historical data from a recent meta-analysis [11] suggest that there may be a longer duration of effect following BPB with LB compared with BPB with immediate-acting local anesthetics, with or without adjuvants, but this will need to be validated by future prospective studies. The difficulty of maintaining patient blinding when using a saline BPB is a further limitation of the placebo-controlled design. However, reporting of transient sensorimotor reduction and the requirement for immobilization of the affected shoulder in both treatment arms suggests that patients and evaluators may not have easily been able to discern if the study drug or placebo was administered. The standardized pain management protocol provided uniform management of postoperative pain during the first 72 hours using acetaminophen and opioids, without adjuvants such as NSAIDs or gabapentinoids. Although robust multimodal analgesic regimens are used in many orthopedic surgery clinical pathways, strict adherence to a specific perioperative analgesia protocol was not possible due to wide variability across sites and between patients. A uniform approach to postoperative pain management was critical to the study, as variability in

treatment between patients and across study sites would have otherwise inevitably confounded the evaluation of efficacy. Although implementing a pain management protocol that disallows NSAIDs may limit the generalizability of this study, restricting adjuvant analgesics helped minimize potential confounding factors, allowing for more accurate efficacy evaluation. Lack of ultrasound assessment for phrenic nerve involvement is also a study limitation. Inclusion of both RCR and TSA could have reduced study power by introducing variation in pain scores. Our study does not provide efficacy data for LB 266 mg, as the small sample size prevented analysis. LB 133 mg resulted in statistically significant improvements vs placebo for the secondary end points; however, these data should be interpreted with caution because the study was not powered for these assessments. Although postsurgical opioid use was assessed through 72 hours postsurgery, these data cannot be extrapolated to estimate future long-term opioid use. The stringent inclusion criteria may limit the applicability of the study results to all populations. However, inclusion of multiple sites, surgeons and anesthesiologists, and a diverse patient population suggests that our findings are generalizable.

Conclusions

LB 133 mg as a single-injection BPB added to a standardized pain management protocol was associated with significantly improved analgesia and reduced opioid consumption through 72 hours after shoulder surgery compared with the standardized protocol alone, while demonstrating a similar safety profile. Importantly, patients who received LB 133 mg were nine times more likely to be opioid-free at 48 hours postsurgery. These findings indicate that LB may provide a valuable therapeutic option as a long-acting single-injection local anesthetic for patients undergoing painful surgical procedures. Future studies should assess the comparative effectiveness vs multimodal analgesia with bupivacaine HCl for major shoulder surgery.

Acknowledgments

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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