Single-Shot Liposomal Bupivacaine Reduces Postoperative Narcotic Use Following Outpatient Rotator Cuff Repair

A Prospective, Double-Blinded, Randomized Controlled Trial

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Background: Liposomal bupivacaine (LB) theoretically is longer-acting compared with conventional bupivacaine. The purpose of this study was to compare conventional bupivacaine combined with dexamethasone (control group), LB combined with conventional bupivacaine (LB group), and LB combined with dexamethasone and conventional bupivacaine (LBD group) in a perineural interscalene nerve block during ambulatory arthroscopic rotator cuff repair to determine if LB decreased postoperative narcotic consumption and pain. The effect of supplemental dexamethasone on prolonging the analgesic effect of LB was also assessed.

Methods: This was a prospective, double-blinded, randomized controlled trial of 76 consecutive patients who underwent outpatient arthroscopic rotator cuff repair. Patients were randomized into the 3 interscalene-block treatment groups: control group (n = 26), LB group (n = 24), and LBD group (n = 26). Outcome measures included pain measured with a visual analog scale (VAS; 0 to 10) and narcotic consumption measured in oral morphine milligram equivalents (MME). Both were measured daily on postoperative day 0 through postoperative day 4.

Results: Generalized estimating equation modeling revealed that narcotic consumption across all time points (postoperative days 0 to 4) was significantly lower in the LB group compared with the control group (mean difference, −8.5 MME; 95% confidence interval, −15.4 to −1.6; p = 0.015). Narcotic consumption was significantly higher in the control group on postoperative days 2 and 3 compared with the LB group (p = 0.004 and p = 0.02, respectively) and the LBD group (p = 0.01 and p = 0.003, respectively). There was no difference in narcotic consumption between the LBD and LB groups on any postoperative day. VAS pain scores in all groups were similar across all postoperative days.

Conclusions: Among patients undergoing outpatient arthroscopic rotator cuff repair, the addition of LB to conventional bupivacaine in interscalene nerve blocks appeared to be effective in controlling postoperative pain. Because LB with and without dexamethasone decreased postoperative narcotic use, LB should be considered for use in preoperative interscalene nerve blocks to reduce the reliance on narcotics for pain management.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Arthroscopic rotator cuff repair as an outpatient surgical procedure has become the norm[1], partially as a result of innovations in pain management, specifically involving regional anesthesia and multimodal techniques. Despite these improvements, uncontrolled postoperative pain remains an issue, leading to prolonged ambulatory stays, patient dissatisfaction, unexpected hospital visits, and increased complications[2-13]. Furthermore, concerns regarding narcotic consumption and addiction have resulted in regulations that make managing postoperative pain more difficult[14].

Interscalene nerve block is a common technique to provide perioperative pain control in shoulder procedures, with good efficacy, low complication rates, and reduced narcotic consumption[15-20]. Although ultrasound assistance to administer

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nerve blocks improves accuracy and provides consistent analgesic effects, the short analgesic duration with conventional local anesthetics remains a major limitation[17,19,21]. Modalities to prolong analgesia include the use of indwelling catheters and the addition of adjuvant perineural dexamethasone[15,16,22-27]. Dexamethasone prolongs block duration when administered via perineural or intravenous routes, but perineural administration is superior in duration[25,28,29].

Liposomal bupivacaine (LB), or Exparel (Pacira Biosciences), is approved for single-shot interscalene administration by the U.S. Food and Drug Administration (FDA)[30]. This medication provides up to 72 hours of extended-release bupivacaine via the multivesicular and honeycomb-like structure that predictably breaks down slowly[31]. Although studies have evaluated the efficacy of local injections of LB in an inpatient setting, few studies have assessed the efficacy of LB for perineural blockade in outpatient shoulder surgery[32-35]. Furthermore, to our knowledge, no study to date has compared the use of LB alone with the use of LB with adjuvant dexamethasone, as the analgesic duration of LB may be further prolonged by dexamethasone, similar to the results described by Rwei et al. in a rat model[29].

The purpose of the present study was to compare conventional bupivacaine combined with dexamethasone, LB combined with conventional bupivacaine (LB group), and LB combined with dexamethasone and conventional bupivacaine (LBD group) in a perineural interscalene nerve block during ambulatory arthroscopic rotator cuff repair to determine if LB decreased postoperative narcotic consumption and pain. We hypothesized that interscalene nerve blocks with LB or LBD would significantly decrease postoperative narcotic use compared with conventional interscalene blocks with bupivacaine and adjuvant dexamethasone. The supplemental effect of dexamethasone in prolonging the analgesic effect of LB was also evaluated.

Materials and Methods

Study Design

In this double-blinded, randomized controlled trial, we compared the use of conventional bupivacaine combined with dexamethasone (control group), LB, and LBD in the setting of outpatient arthroscopic rotator cuff repair. Study enrollment occurred between November 13, 2018, and January 17, 2020. The study was approved by the Indiana University institutional review board and was registered at www.clinicaltrials.gov (NCT03822182). The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Fig. 1). No changes to methods or outcomes were implemented following commencement of the study.

Study Population

Patients with rotator cuff tears amenable to arthroscopic repair were identified in the ambulatory-office setting by a single surgeon. Patients were enrolled consecutively to prevent selection bias. Patients were included according to the following criteria: age 18 years or older, English speaking, primary diagnosis of rotator cuff tear, ability to complete surveys by sending and receiving text messages, and ability to provide informed consent. Patients were excluded according to the following criteria: allergies to study medications, known narcotic or alcohol abuse, revision rotator cuff repair, repair performed in a hospital setting rather than an outpatient surgical center, contraindication to regional anesthesia, current narcotic regimen, existing contract with a pain specialist, and diagnosis of coagulation disorder or diabetes. The surgeon provided interested patients with study details including risks, benefits, procedures involved, and the voluntary nature of participation. Patients provided written informed consent during the office visit.

Interventions and Procedures

All patients received a preoperative interscalene block. Study participants were randomized into 1 of 3 nerve block groups. The control group received 30 mL of 0.5% bupivacaine and 0.4 mL (4 mg) of preservative-free dexamethasone. The LB group received 15 mL of 0.5% bupivacaine, 10 mL (133 mg) of LB, and 5.4 mL of normal saline solution. The LBD group received 15 mL of 0.5% bupivacaine, 10 mL (133 mg) of LB, 0.4 mL (4 mg) of dexamethasone, and 5 mL of normal saline solution. The dose of LB in this protocol is the same dose that was utilized in the protocol (Study 402C-327) that received approval from the FDA for LB in interscalene nerve block[30]. Bupivacaine was added to groups 2 and 3 in order to provide immediate onset of pain relief, allowing for better anesthetic management during and immediately following the surgical procedure. Normal saline solution was added to groups 2 and 3 to have an equal injectable volume in each group to prevent volume-related variance of local anesthetic spread between groups. All surgical procedures were performed in a single outpatient surgical center. All patients received a general anesthetic maintained with sevoflurane or desflurane, nausea prophylaxis with 4 mg of ondansetron and 4 mg of dexamethasone, and a single 15-mg intravenous dose of ketorolac. No local anesthesia was utilized by the treating surgeon. All rotator cuff tear repairs were performed arthroscopically with use of a double-row configuration. In all patients with an intact long head of the biceps tendon, an arthroscopic biceps tenotomy or tenodesis was performed. Postoperatively, all operative arms were immobilized in a sling, with only elbow and wrist motion allowed.

Randomization

Twenty-six identifiers of each group were individually sealed in 78 total envelopes. Envelopes were randomly chosen and opened by the anesthesiologist prior to the surgical procedure. After determining the treatment group, the anesthesiologist added the name of the patient back to the envelope. Sealed envelopes were stored in a locked container, only accessible by the chief of staff, and the envelopes were only opened at the completion of the study. To blind the surgeon and patient, nerve blocks were prepared and performed under anesthesia by the anesthesiologist prior to the surgeon entering the room. It was not feasible to blind the anesthesiologist because LB is a cloudy fluid, unlike conventional bupivacaine; it was also not possible to have the same anesthesiologist for each procedure, although this study involved a core team

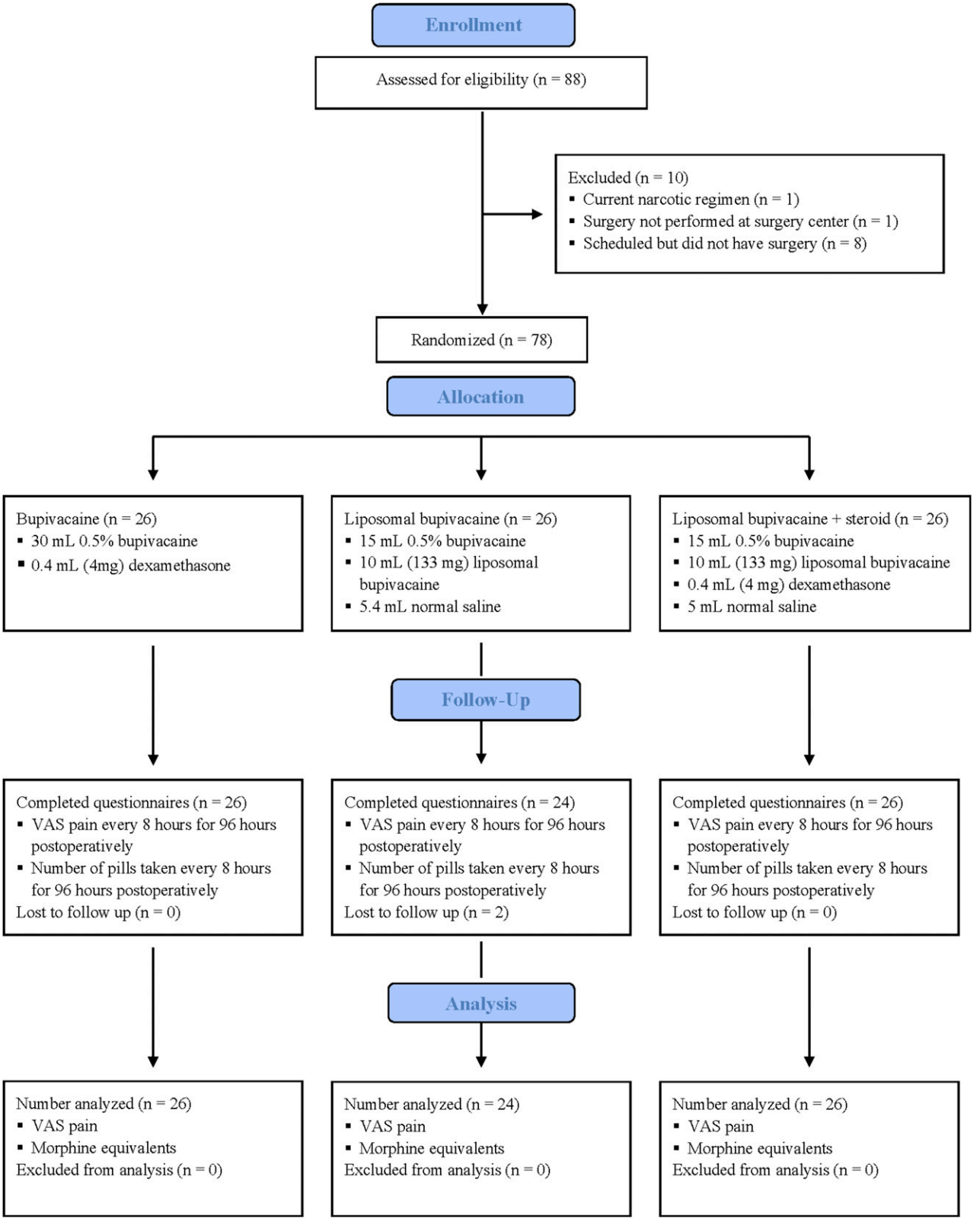

Fig. 1

CONSORT flow diagram.

of experienced anesthesiologists. The method of administration and total volume of medication administered were the same in all groups. Postoperatively, all patients received the same narcotic pain regimen (5-mg oxycodone instant-release tablets, 1 taken orally every 4 hours as needed for pain) and were instructed to abstain from any additional analgesics or anti-inflammatories.

Study Outcomes

The primary outcome measure was postoperative opioid use, converted to morphine milligram equivalents (MME) measured at each postoperative day (POD). Daily postoperative patient-reported visual analog scale (VAS) pain (rated numerically by patients on a scale from 0 to 10, with 0 representing no pain and 10 representing maximum pain) was included as a secondary outcome measure.

Data Collection

This study utilized CareSense (Medtrak, Inc.), a password-protected and Health Insurance Portability and Accountability Act-compliant program, for data collection. Patients were assigned an identifier, and primary data were collected, stored electronically, and encrypted. Only the principal investigator had access to the database. At the conclusion of the study, deidentified data were exported to an encrypted Excel (Microsoft) file on a password-protected computer. Variables collected included age, sex, type of tear, date of the surgical procedure, number of anchors, concomitant procedures, preoperative and postoperative VAS pain score, and number of narcotic pills ingested. Patients were prompted to provide VAS pain scores and the number of narcotic pills ingested every day at 8 A.M., 2 P.M., and 8 P.M. via text message. If no message was received, a telephone call was made by study personnel to obtain the information. Patients without smartphones recorded VAS pain scores and narcotic consumption in a personal log. Data were collected on POD 0 through 4.

Sample Size

Previous studies have shown large effect sizes when comparing daily postoperative VAS pain scores and cumulative narcotic use between LB and a control group[34,35]. Differences in these measures have not been reported between LB and LBD, but these differences were expected to be smaller than that observed when comparing LB and a control group. A sample size of 22 participants per group would be required, based on a repeated-measures analysis of variance with 3 groups and an effect size of $f = 0.30$, $\alpha = 0.05$, $\beta = 0.2$, and 5 repeated measures with a correlation between measures of $r = 0.5$. To account for 15% attrition, a total of 26 patients per group were included, yielding a total of 78 participants.

Statistical Analysis

Patient characteristics were compared between treatment groups with use of chi-square or Fisher exact tests for categorical variables and analysis of variance or Kruskal-Wallis tests for continuous variables. To account for repeated measures on consecutive PODs, MME-use and VAS-pain outcomes were evaluated with use of generalized estimating equations with least-significant-difference pairwise comparisons; age and number of anchors used for tendon repair were included as covariates. Data were analyzed with use of SPSS (version 25; IBM). All statistical tests were 2-tailed. Significance was set at 0.05.

Results

Seventy-six of 78 patients fully participated in reporting postoperative pain and narcotic usage and were included in the analysis. Twenty-six patients were in the control group, 24 were in the LB group, and 26 were in the LBD group. Participants had a mean age (and standard deviation) of 57.8 ± 9.0 years. Groups were similar with respect to demographic, diagnostic, and treatment characteristics (Table I).

TABLE I Patient Demographics*

	Control Group (N = 26)	LB Group (N = 24)	LBD Group (N = 26)	P Value
Age* *(yr)*	59.1 ± 9.0	56.9 ± 9.6	57.5 ± 8.8	0.68
Male sex†	15 (58%)	14 (58%)	12 (46%)	0.62
Preoperative VAS pain‡	7 (5-8)	6.5 (5-8)	7 (5-8)	0.75
Type of tear†				0.44
Small (<1 cm)	4 (15%)	6 (25%)	4 (15%)	
Medium (1to <3 cm)	18 (69%)	14 (58%)	18 (69%)	
Large (3-5 cm)	0 (0%)	0 (0%)	2 (8%)	
Massive (>5 cm)	4 (15%)	4 (17%)	2 (8%)	
Biceps procedure†				0.27
Tenodesis	8 (31%)	15 (63%)	12 (46%)	
Tenotomy	15 (58%)	8 (33%)	12 (46%)	
Prior rupture	3 (12%)	1 (4%)	2 (8%)	
No. of anchors‡	4 (4-5)	4 (4-5)	4 (4-5)	0.49

*Values are given as the mean and standard deviation. †Values are given as the number of patients, with the percentage in parentheses. ‡Values are given as the median, with the interquartile range in parentheses.

Narcotic Use

Generalized estimating equations factoring in all time points showed that narcotic consumption over time was significantly lower in the LB group compared with the control group (mean difference, −8.5 MME; 95% confidence interval [CI], −15.4 to −1.6; p = 0.015). There were no significant differences over time between the LB and LBD groups or the LBD and control groups. Generalized estimating equation pairwise comparisons at each time point showed a significant association between treatment group and POD (Fig. 2). Narcotic consumption was significantly greater in the control group on POD 2 and POD 3 compared with the LB group (POD 2 mean difference, 16.6 MME; 95% CI, 5.3 to 28.0; p = 0.004; POD 3 mean difference, 13.8 MME; 95% CI, 2.3 to 25.4; p = 0.02) and LBD group (POD 2 mean difference, 14.0 MME; 95% CI, 3.3 to 24.6; p = 0.01; POD 3 mean difference, 16.3 MME; 95% CI, 5.5 to 27.0; p = 0.003). There was no difference in narcotic consumption between the LB and LBD groups overall or on any individual POD. Pairwise comparisons of narcotic consumption across POD 1 through 4 were similar for the LB group, whereas the LBD group showed a significant decrease in narcotic consumption from POD 2 to 3 (mean difference, −8.5 MME; 95% CI, −14.1 to −2.9; p = 0.003).

VAS Pain

VAS pain scores were similar for all treatment groups across POD 0 through 4, adjusting for age and number of anchors used for tendon repair. Pairwise comparisons revealed that the LBD group had significantly less pain on POD 3 compared with the LB group (mean difference, −1.0; 95% CI, −1.9 to −0.08; p = 0.03) (Fig. 3).

Discussion

This double-blinded, randomized controlled trial showed that a preoperative interscalene nerve block with LB for outpatient arthroscopic rotator cuff repairs reduces the amount of narcotics consumed from POD 1 through 4 compared with a standard interscalene nerve block with bupivacaine and adjuvant dexamethasone. There was no overall difference in VAS pain score across treatment groups, suggesting that patients in the control group likely used additional oral pain medicine to achieve similar pain relief compared with those in the LB and LBD groups. The effect of LB and LBD on reducing narcotic consumption was most pronounced after POD 1, likely because of the fact that an interscalene block with conventional bupivacaine and dexamethasone has a duration of effect up to 24 to 48 hours[25,28,29]. For POD 1 through 3, patients who received a block containing LB required roughly 33% fewer MME compared with those in the control group. Given that a single oxycodone 5-mg tablet is 7.5 MME[36], patients who received LB consumed about 4 to 6 fewer narcotic pain pills on POD 1 through 3.

In patients with glenohumeral arthritis treated with primary shoulder arthroplasty and in patients with rotator cuff disease treated nonoperatively, the minimal clinically important

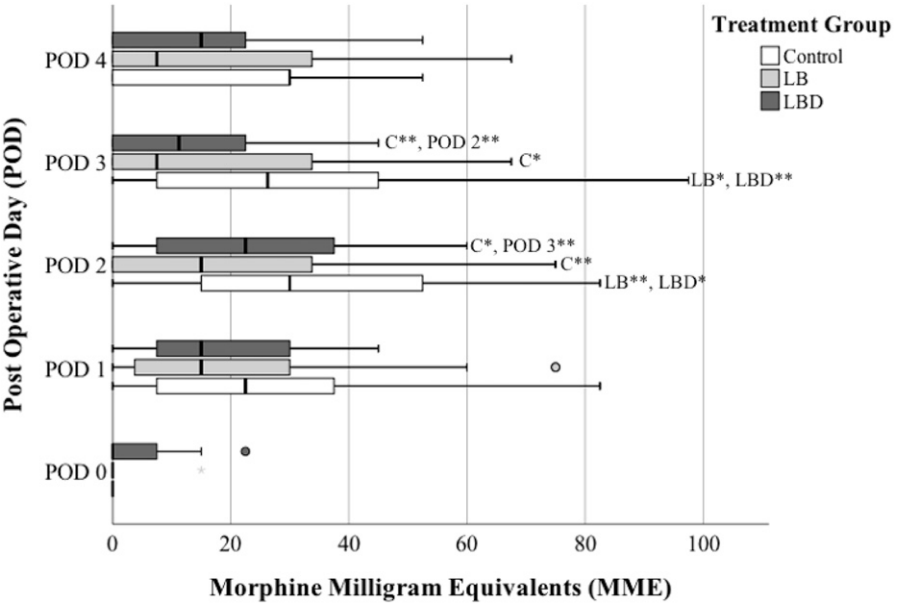

Fig. 2

Box plot showing mean narcotic consumption in MME by treatment group and POD. Generalized estimating equations with least-significant-difference pairwise comparisons identified significant differences between treatment groups and between PODs (adjusted for age and number of anchors). The boxes represent the first through third quartile values, with a vertical line representing the median. The bars represent the minimum and maximum values. Outliers are represented by circles. Bars labeled with C (control), LB, and LBD indicate significant differences between treatment groups on the same POD. Bars labeled with POD 0 through 4 indicate significant differences within the same treatment group between 2 different PODs. There was a significant reduction in MME in the LB and LBD groups compared with the control group on POD 2 and POD 3. Within the LBD group, there was a significant reduction in MME between POD 2 and POD 3. *P < 0.05. **P < 0.01.

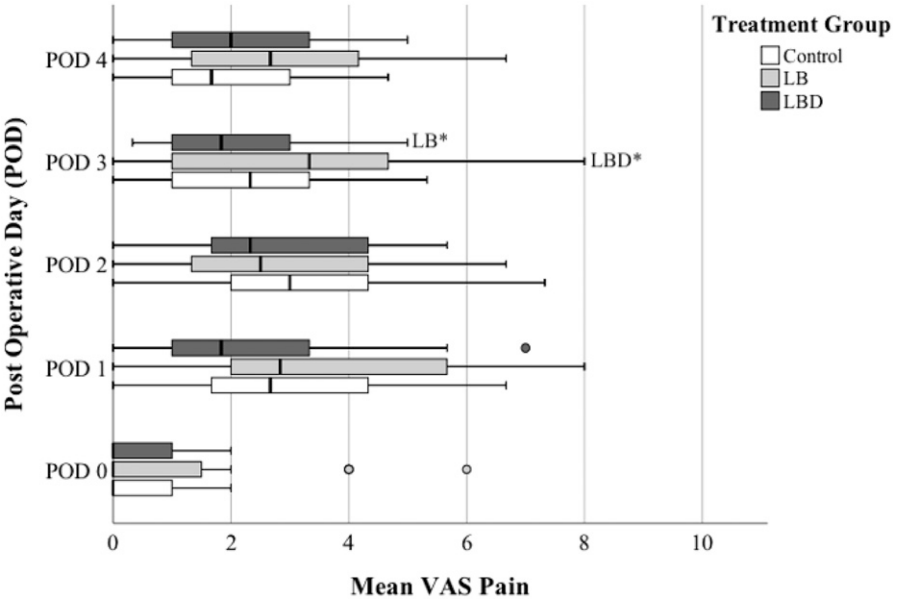

Fig. 3

Box plot showing mean VAS pain by treatment group and POD. Generalized estimating equations with least-significant-difference pairwise comparisons identified significant differences between treatment groups and between PODs (adjusted for age and number of anchors). The boxes represent the first through third quartile values, with a vertical line representing the median. The bars represent the minimum and maximum values. Outliers are represented by circles. Bars labeled with LB and LBD indicate significant differences between treatment groups on the same POD. VAS pain scores remained similar between all groups, with the exception of the LBD group having a significantly lower average score compared with the LB group on POD 3. *P < 0.05.

difference in VAS pain scores is 1.4 points[37,38]. Although VAS pain scores were similar between the LB and control groups, scores were 1.0 point lower in the LBD group compared with the LB group on POD 3, suggesting that the addition of dexamethasone resulted in a prolonged analgesic effect. Although significant, this difference did not meet the threshold for clinical importance. By POD 4, there was no difference in pain scores across groups, suggesting a cessation of the supplemental analgesic effect of dexamethasone without rebound pain.

Several studies have examined periarticular injections containing LB in shoulder arthroplasty[39]. Okoroha et al. showed a significant increase in narcotic use and VAS pain score on POD 0 among patients who received periarticular LB infiltration compared with those who received a preoperative bupivacaine interscalene block; both groups reported similar pain relief thereafter[40]. In a similar study by Namdari et al., patients who received a local LB injection had higher VAS pain scores within the first 8 hours after the surgical procedure compared with patients who received a preoperative bupivacaine interscalene block; however, pain scores among patients who received a block surpassed those of patients who received a local injection at 24 hours postoperatively[41]. In another study, Namdari et al. also showed that, in addition to a standard interscalene block, local infiltration of LB offered no improvement in VAS pain scores at 72 hours postoperatively and was associated with an increase in narcotic consumption on POD 1[42]. Sabesan et al. compared interscalene blocks with bupivacaine and supplemental local infiltration of LB to continuous interscalene bupivacaine catheters. In that study, patients who received LB had fewer complications, lower overall cost, and equivalent narcotic use and pain scores within the first 24 hours postoperatively[43]. These outcomes became equivalent between treatment groups after 24 hours. Contrary to this, Abildgaard et al. found that patients with continuous interscalene bupivacaine catheters had better pain scores than those patients who received periarticular LB infiltration during POD 0, with this outcome becoming equivalent thereafter. Furthermore, patients who received a periarticular LB injection required more opioids during the hospital admission[44].

Two studies have examined the effect of interscalene nerve blocks with LB in rotator cuff repair. In patients who received preoperative interscalene nerve blocks with LB compared with conventional bupivacaine blocks, Shariat et al. showed that there was a decrease in the number of oxycodone-acetaminophen tablets taken and that the quality of analgesia may have been better within PODs 1 to 3 following rotator cuff repair, but not at POD 7[45]. Vandepitte et al. similarly showed that the addition of LB to conventional bupivacaine in interscalene nerve blocks may decrease pain within the first postoperative week for both shoulder arthroplasty and rotator cuff repair[46]. The present study supports that there was an overall decrease in the consumption of narcotics postoperatively among patients who received LB, with similar pain scores between all groups, indicating that LB blocks contributed to a reduction in postoperative pain.

This study had several limitations. Firstly, we did not include a cost analysis. LB at our institution is approximately $200 USD per vial. Although not substantial, the financial impact of block medication needs to be weighed against patient

satisfaction and lessened narcotic consumption. Secondly, multiple unblinded anesthesiologists administered the blocks. Slight variation in technique could create variation in block efficacy. Thirdly, pain is subjective and can vary from individual. Additional psychosocial factors could have affected narcotic use and pain response. Although MME dosing is believed to have a stronger correlation to pain, as it is less subjective, we attempted to control for variation in VAS pain scores by collecting 3 daily measures and adjusting our statistical analysis for the number of anchors used in the tendon repair in order to account for the impact that tear size and pattern or complexity of surgical repair could have had on narcotic consumption and VAS pain. Finally, we did not control for variations in management of the biceps tendon. Although clinical outcomes are similar between tenotomy and tenodesis, Belay et al.[47] demonstrated that tenotomy may lead to earlier improvement in pain, although the study did not exclusively include patients treated for rotator cuff repairs as did ours.

Among patients who underwent outpatient arthroscopic rotator cuff repair, the addition of LB to conventional bupivacaine in an interscalene nerve block appeared to effectively decrease postoperative pain. Since LB significantly decreased postoperative narcotic use, LB should be considered for use in preoperative interscalene nerve block to reduce the reliance on narcotics for pain management. The addition of dexamethasone to LB prolonged the analgesic effect but did not meet the minimal clinically important difference. ■

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