



Article

Opioid Sparing at 24 h after Total Shoulder Arthroplasty by Undiluted Liposomal Bupivacaine Single Shot Interscalene Block: A Randomized Clinical Trial, First Results

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Abstract: Background: The purpose of this study was to compare postoperative opioid consumption following total shoulder arthroplasty, after: (A) a single-shot undiluted liposomal bupivacaine (LB; commercial name: Exparel) interscalene block, or (B) a Ropivacaine block (R), supplemented with continuous catheter infusion. Methods: This prospective, randomized study (NCT03739021) compared postoperative analgesic requirements in Morphine Milligram Equivalent (MME) during the first 24 h after discharge from the post-anesthesia care unit (PACU) in patients receiving total shoulder arthroplasty. Two similar groups of 30 patients each received equivalent general operative anesthesia. Preoperative interscalene block was performed with either 10mL of undiluted liposomal bupivacaine (LB) or ropivacaine (R) 0.5% plus continuous catheter infusion. Results: There were no differences between the two groups regarding age, gender, length of surgery, intraoperative narcotic usage, or length of hospital stay. The time required to administer (LB) compared to (R) was significantly reduced (5 min vs. 15 min). The LB group experienced a reduction in MME during the first 24 h after PACU discharge (25 vs. 41 MME). Conclusion: A single shot of undiluted liposomal bupivacaine (LB) provided a significant ($p = 0.045$) reduction in opioid use during the first 24 h after shoulder replacement surgery compared to ropivacaine (R) with continuous catheter infusion. A larger sample group will be required to bolster these results. There was no measured difference in reported pain level. LB also took less time to administer.

Keywords: liposomal bupivacaine; ropivacaine continuous infusion; randomized clinical trial; shoulder replacement; opioids for postoperative pain control

1. Introduction

Joint replacement procedures such as total shoulder arthroplasty (TSA) can lead to significant pain in the early postoperative period. Adequate pain control following TSA is beneficial not only for patient comfort but also to facilitate early therapy and rehabilitation exercises, which have been shown to improve outcomes and functional recovery [1]. Postoperative pain following TSA has commonly been managed with opioids. However, in recent years, concerns regarding the overuse of opioids and their unwanted side effect profile, including respiratory depression, nausea/vomiting, and drug dependence, have popularized the use of a multimodal approach to analgesia. Pain medications from different classes such as acetaminophen, non-steroidal anti-inflammatory drugs, antiepileptics, antidepressants, and local/regional anesthetics are given in various combinations.

Together, these pharmacologic methods may act to decrease overall opioid requirements. Practice guidelines from the American Society of Anesthesiologists (ASA) support the use of multimodal analgesia in postoperative pain management whenever possible [2,3].

Exparel is a form of liposomal bupivacaine (LB), a long-acting local anesthetic with analgesic effects exceeding 24 h [4]. LB increases the duration of action of traditional bupivacaine by loading the anesthetic into multivesicular liposomes: this process slows the release of medication into the tissues and delays peak plasma concentrations [4]. This allows for sustained pain control beyond the 2–8 h duration that local anesthetics would typically be expected to last. LB was initially approved for FDA use in 2011 to provide postsurgical analgesia into surgical sites and received subsequent approval in 2018 for a new indication, as an interscalene brachial plexus block following shoulder surgery. While its longer duration of action should offer an intuitive advantage in managing pain, previous studies on the effect of liposomal bupivacaine on postoperative opioid consumption following shoulder surgery have produced conflicting results [5–9]. This study prospectively compares the effects of a single shot of undiluted LB interscalene block to a ropivacaine block, supplemented with a continuous catheter infusion of ropivacaine, on postoperative opioid use following total shoulder arthroplasty.

2. Methods

This was a prospective, randomized study pre-registered on the National Clinical Trials Registry (NCT03739021). We estimated a sample size to provide an excess of 20% difference in postoperative opioid requirements between the LP and the R groups, calculated from published data [4] and our current experience: this suggested two groups of 25 patients, which we expanded to 30 patients per group to account for the variability of analgesic requirements. Details about the required number of patients is added in the supplementary section (Table S1) Randomization was obtained via SAS version 9.4 as 6 repetitions of 10 patients each, randomized between LB and R, and configured into a set of 60 sequenced opaque envelopes. The study team assessed 61 patients undergoing primary and revision shoulder arthroplasty (Figure 1).

Of the 61 patients assessed for eligibility, one was excluded for change in surgical procedure. The remaining 60 patients were randomly allocated to either Exparel or Ropivacaine with continuous catheter infusion. One patient was consented but was later excluded because his surgery was modified during the procedure to debridement of infected revision, in lieu of full arthroplasty. The 60 patients were randomized to receive preoperative ultrasound-guided interscalene blocks, with either a single-shot of 10 mL of undiluted LB (133 mg) or ropivacaine (R) (0.5%, 20 mL bolus, followed by continuous catheter infusion at 5 mL/hour of ropivacaine 0.2%. This was followed by 2.5 mL on-demand boluses). All patients received similar general endotracheal anesthesia for the procedure. The characteristics of the two patient groups are detailed in Table 1.

Table 1. Characteristics of the two patient groups.

Anesthetic	Approximate Block Procedure Duration (Minutes)	Gender (Male/Female)	Age	Surgery Duration (Minutes)	Hospital Stay (Days)	Intra-Op Narcotic (MME)	PACU Narcotic (MME)
Exparel	5	20/10	M	67.4	209.3	1.3	5.2
			SD	9.4	37.6	0.7	6.9
Ropivacaine	15	17/13	M	70.8	199.3	1.5	3.7
			SD	6.9	37.5	0.9	6.4
Significance			NS	NS	NS	NS	NS

M: Mean; SD: standard deviation; NS: Non-significant, MME: Morphine milligram equivalent, Intra-op: Intra-operative; PACU: post-anesthesia care unit.

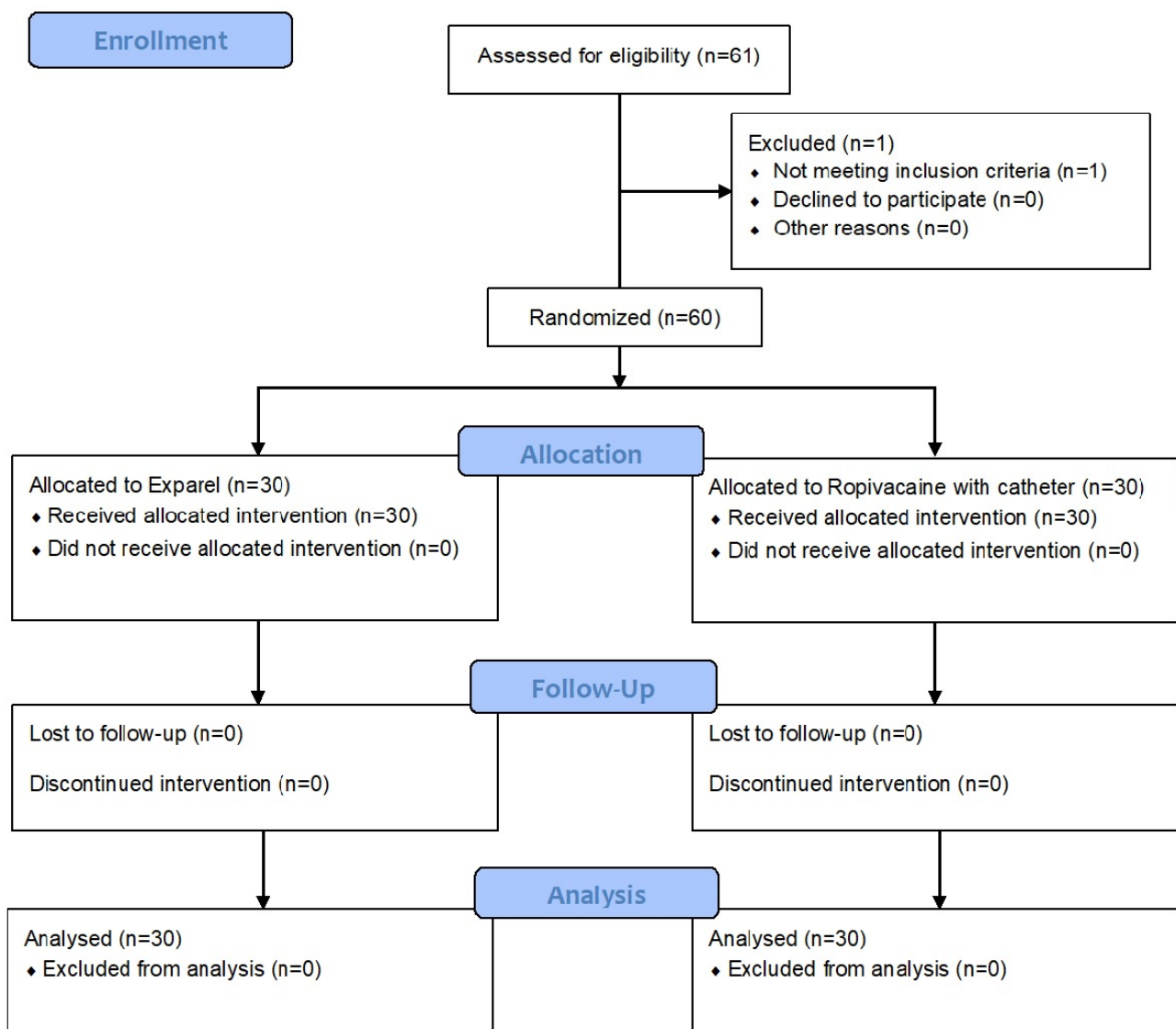


Figure 1. Flow chart demonstrating study design.

2.1. Technique of Block Administration

All blocks for the study were performed by an experienced regional anesthesia team physician. After randomization to determine the block technique, the patient was positioned and prepped using chlorhexidine or alcohol solution, with the head turned toward the contralateral shoulder. A 'Time-Out' safety check was then performed before sedation with 2–4 mg intravenous midazolam. All blocks were performed using the sterile technique, and standard ASA monitors were present and used. The brachial plexus was visualized via ultrasound using a 15–6 MHz linear probe by first placing the probe superior to the clavicle and locating the subclavian artery and the accompanying brachial plexus trunks. The ultrasound was then translated cranially until the brachial plexus was visualized between the anterior and middle scalene muscles. The block was then performed using the appropriate technique for the patients' randomized group.

For the patient group selected to receive LB, a 20G short bevel block needle was inserted and advanced immediately adjacent to the brachial plexus, using 1–2 mL normal saline for hydro-dissection if needed, depending on patient anatomy. A dose of 10 mL of LB was then incrementally injected into the desired area while observing appropriate spread under ultrasound. The needle was then removed, and the patient proceeded to the operating room (OR) shortly thereafter.

For the patient group selected to receive ropivacaine with an accompanying nerve block catheter, the insertion site was anesthetized with 1% lidocaine before a 17G Touhy was inserted and advanced immediately adjacent to the brachial plexus. Twenty mL 0.5% ropivacaine was then incrementally injected, while observing appropriate spread with ultrasound visualization. A 19G catheter was then advanced through the needle, and catheter tip placement was confirmed using ultrasound and incremental normal saline injections. A test dose of 5 mL, 1.5% lidocaine with epinephrine 1:200,000, was then given through the catheter to further confirm placement. The catheter was then secured, and an infusion pump containing 0.2% ropivacaine was connected using standardized settings of 5 mL/h infusion with 2.5 mL demand bolus available every 30 min for a maximum hourly dose of 10 mL/h. The patient then proceeded to the OR shortly after the conclusion of block placement. Ropivacaine was utilized for the continuous infusion group in order to avoid potential cardiotoxicity of prolonged bupivacaine infusion. All block procedures were completed by one of two pain fellows who had completed anesthesiology residency and were in the 5th post-graduate of training, under the direct supervision of an experienced regional anesthesia provider, board-certified in anesthesiology for over 5 years. Postoperative pain evaluation was conducted using the Visual Analog Scale (0–10 points); patients were asked about their pain levels upon discharge from the PACU, as well as every 4 h during hospital stay. These evaluations were reported in their charts.

2.2. Statistical Analysis

Details of the critical study patient numbers are summarized in the supplementary section. The primary endpoint measured was opioid use in morphine milligram equivalents (MME) at 24, 36, 48, and 72 h following PACU discharge. The statistical comparison at 24 h comprised all sixty patients and utilized unpaired *t*-test via SPSS software. Comparison at later times was not possible due to a much-reduced number of patients. Secondary endpoints included time to perform the nerve block, intraoperative narcotic use in MME, length of hospital stay, and postoperative inpatient pain scores.

3. Results

On average, the time needed to perform the nerve block was significantly shorter for LB injection: 5 min vs. 15 min for catheter insertion. There were no differences between the groups for age, gender, surgery duration, intraoperative opioid usage, or length of hospital stay (Table 1). In terms of ASA Physical Status Classification, the LB group comprised 3 ASA II, 26 ASA III, and 1 ASA IV patients. The R group enrolled six ASA II, 23 ASA III, and 1 ASA IV patient. These distributions were non-significantly different ($X^2 = 1.18$; $p = 0.55$). The distribution of primary arthroplasty vs. revision procedure was 7 vs. 23 in the Exparel group and 3 vs. 27 in the ropivacaine group. The 7 Exparel revision patients required 35.5 MME in the first 24 h, while the three revision patients in the ropivacaine group required 47.3 MME.

All 60 randomized patients received treatment and were observed after PACU discharge for a minimum of 24 h. Two patients in the R group had their catheters removed after the first 24 h: one of these patients reported shortness of breath, possibly due to phrenic nerve block with diaphragmatic paralysis. The second reported generic “chest pains”. Both patients were evaluated and determined to be clinically stable after stopping the local infusion and removing the catheter. No other patients reported complaints in either group.

Patients receiving LB required significantly fewer opioids in the first 24 h after discharge from PACU, compared to those receiving ropivacaine (24.8 ± 19.2 vs. 41.1 ± 39.3 MME). The statistical significance was tempered by the large variability observed in the two groups. Furthermore, postoperative opioid requirements at subsequent time points could not be analyzed due to the reduced number of patients still hospitalized, leading to insufficient power analysis (Table 2). Therefore, a comparison was not applicable beyond 24 h, though

a similar trend was still visible at 36 h. Finally, no significant difference in postoperative pain levels between the two groups was reported at 24 h (LB: 3.4 ± 1.9 vs. R: 3.6 ± 1.8).

Table 2. Morphine milligram equivalents (MME) measured at postoperative times after PACU discharge.

Anesthetic		24 h (MME)	36 h (MME)	48 h (MME)	72 h (MME)
Exparel	# of patients hospitalized	30	5	5	5
	M	24.8	10.9	45	28.9
	SD	19.2	7.4	67.8	24.5
Ropivacaine	# of patients hospitalized	30	11	11	7
	M	41.1	35.5	13.2	58.9
	SD	39.3	28.7	9.8	59.2
<i>p</i> -value:		0.045	NA	NA	NA

MME values at 24, 36, 48, and 72 h after PACU discharge. Note that all 60 patients are counted only at 24 h. A decreasing number of patients were still in hospital after the 24 h period. A 40% reduction in MME was noted at 24 h after Exparel block. M: Mean; SD: Standard deviation; #: Number, N/A: Not Applicable.

4. Discussion

Our data indicate that a preoperative single-shot interscalene block with liposomal bupivacaine, compared to continuous ropivacaine block, leads to a significant reduction in opioid consumption within the first 24 h following PACU discharge (24.8 ± 19.2 vs. 41.1 ± 39.3 MME). These results align with the purpose of multimodal analgesia, which has demonstrated opioid-sparing effects in the postoperative period [6]. However, previous reports, specifically on the impact of LB on postoperative opioid consumption following shoulder surgery, have produced conflicting data. Sabesan et al. found that in comparing LB versus continuous interscalene catheter after TSA, both groups had equivalent opioid use, pain scores, and time to the first opioid rescue within the first 24 h [8]. Similarly, in their meta-analysis, Kolade et al. 2019 determined comparable pain scores and opioid consumption between patients receiving LB or non-liposomal local anesthetic agents after shoulder surgery [5]. However, Namdari et al. concluded that patients receiving LB interscalene blocks for TSA required significantly more postoperative opioids. The use of LB did not significantly decrease pain scores within the first 72 h [7]. This is in contrast to Mandava et al. 2020, which reported that the use of LB interscalene blocks led to improved postoperative pain and decreased opioid consumption versus standard interscalene nerve block [6]. The present study further supports administering LB to spare the use of opioids in the early recovery period after TSA. This was carried out while achieving comparable pain scores (E: 3.4 ± 1.9 vs. R: 3.6 ± 1.8) in both groups, despite the significant reduction in postoperative opioid consumption.

In addition to its opioid-sparing effect, an interscalene block with a single injection of LB also avoids the insertion of a continuous catheter, which offers disadvantages and increases the risk of certain complications. These include possible catheter dislodgment or migration, fluid leakage, infection, and nerve injury. A single injection also confers advantages in workflow and resource utilization. On average, we demonstrated that an LB injection can be performed in 5 min, compared to 15 min for insertion of an interscalene catheter. This 10 min time saving does not also account for the additional equipment and nursing support required to maintain the proper and functional operation of a continuous catheter for the duration of its use.

At the time of this publication, a single 10 mL (133 g) dose of Exparel costs 189.37 USD, significantly more than the estimated 1–3 USD for the same dose of standard bupivacaine [10]. However, the additional cost of medication should also be considered, along

with any cost savings from improved OR/PACU efficiency or decreased hospital length of stay and reduced equipment and personnel required by continuous catheter maintenance. In the present study, the time needed to administer an LB interscalene block was 10 min shorter than a ropivacaine block (5 min vs. 15 min, $p < 0.02$). This time savings corresponds to a ten-minute shorter procedure duration. In our institution, the block procedure insertion and setup are commonly completed in a block induction area where the utilization cost is less than the running costs of the OR. However, the staffing costs are still elevated at the same level as the recovery room [11,12]. However, Ali et al. recently reported longer average PACU stays for patients receiving LB versus ropivacaine, a finding attributed to the slower efficacy of LB [9]. We did not collect the length of stay of our two groups of patients and cannot comment on this difference. Additional research would further elucidate the effects of LB on OR/PACU workflow. A larger number of patients studied will be needed to reach a more robust difference between the two groups, which might allow to demonstrate a significant difference in hospital length of stay. However, this is an important factor that would further inform a cost–benefit analysis. Cohen 2012 conducted a health economic trial reporting a significantly lower average cost of hospitalization (8766 USD vs. 11,850 USD) and median length of hospital stay (2.0 days vs. 4.9 days) in patients receiving multimodal analgesia with LB, compared to patient-controlled analgesia with opioids [13]. Similarly, Kirkness et al. 2016 reported a total direct hospital cost savings of almost 500 USD per patient using LB vs. standard bupivacaine for total knee arthroplasty. Furthermore, significantly more LB patients (50% vs. 19%) were discharged within the first two days [14].

Common side effects of LB include nausea, vomiting, constipation, headache, and pyrexia. Compared to standard bupivacaine HCl, LB confers no additional risks in terms of safety, side effect profile, wound/bone healing, and cardiotoxicity [15–20]. However, care should be taken to avoid co-administration with other local anesthetics and antiseptics, as this may increase the release of bupivacaine from liposomes [4]. In addition, patients' ASA scores should also be considered, as they may predict complications following LB interscalene block [21]. However, ASA scores between our two groups were comparable.

Limitations of the current study include single-site data collection, response bias for patients self-reporting pain scores, and an insufficient sample size for postoperative follow-up after the first 24 h. Future studies can consider further measuring patient satisfaction, shoulder surgery outcomes, and enrolling more patients for data on hospital length of stay and opioid consumption beyond the first 24 h.

5. Conclusions

A single shot of undiluted injection of liposomal bupivacaine provided a significant reduction in opioid use during the first 24 h after shoulder replacement surgery compared to a plain ropivacaine block with continuous catheter infusion, with no difference in pain control and patient satisfaction. Liposomal bupivacaine also took significantly less time to administer and utilized fewer resources.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/surgeries3010008/s1>, Table S1. Individual values for MME (Morphine Milligram Equivalent) for the first 24 h for the two groups of 30 patients.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the University of South Florida (Pro00037089 approved on 10 December 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All of the data collected are available by corresponding author after reasonable request.

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