

Liposomal Bupivacaine vs Interscalene Nerve Block for Pain Control After Shoulder Arthroplasty: A Retrospective Cohort Analysis

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Abstract

The aim of this study was to compare liposomal bupivacaine and interscalene nerve block (ISNB) for analgesia after shoulder arthroplasty. We compared 37 patients who received liposomal bupivacaine vs 21 who received ISNB after shoulder arthroplasty by length of hospital stay (LOS), opioid consumption, and postoperative pain. Pain was the same in both groups for time intervals of 1 hour and 8 to 14 hours postoperatively. Compared with ISNB patients, liposomal bupivacaine patients reported less pain at 18 to 24 hours

($P = .001$) and 27 to 36 hours ($P = .029$) and had lower opioid consumption on postoperative days 2 ($P = .001$) and 3 ($P = .002$). Mean LOS for liposomal bupivacaine patients was 46 ± 20 hours vs 57 ± 14 hours for ISNB patients ($P = .012$). Sixteen of 37 liposomal bupivacaine patients vs 2 of 21 ISNB patients were discharged on the first postoperative day ($P = .010$). Liposomal bupivacaine was associated with less pain, less opioid consumption, and shorter hospital stays after shoulder arthroplasty compared with ISNB.

The annual number of total shoulder arthroplasties (TSAs) is rising with the growing elderly population and development of new technologies such as reverse shoulder arthroplasty.¹ In 2008, 47,000 shoulder arthroplasties were performed in the US compared with 19,000 in 1998.¹ As of 2011, there were 53,000 shoulder arthroplasties performed annually.² Pain control after shoulder procedures, particularly TSA, is challenging.³

Several modalities exist to manage pain after shoulder arthroplasty. The interscalene brachial plexus nerve block is considered the “gold standard” for shoulder analgesia. A new approach is the periarticular injection method, in which the surgeon administers a local anesthetic intraoperatively. Liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, Inc.) is a nonopioid anesthetic that has been shown

to improve pain control, shorten hospital stays, and decrease costs for total knee and hip arthroplasty compared with nerve blocks.⁴⁻⁶ Patients who were treated with liposomal bupivacaine consumed less opioid medication than a placebo group.⁷

Our purpose was to compare intraoperative local liposomal bupivacaine injection with preoperative single-shot interscalene nerve block (ISNB) in terms of pain control, opioid use, and length of hospital stay (LOS) after shoulder arthroplasty. We hypothesized that patients in the liposomal bupivacaine group would have lower pain scores, less opioid use, and shorter LOS compared with patients in the ISNB group.

Methods

A retrospective cohort analysis was conducted with 58 patients who underwent shoulder arthro-

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plasty by 1 surgeon at our academically affiliated community hospital from January 2012 through January 2015. ISNBs were the standard at the beginning of the study period and were used until Exparel became available on the hospital formulary in 2013. We began using Exparel for all shoulder arthroplasties in November 2013. No other changes were made in the perioperative management of our arthroplasty patients during this period. Patients who underwent TSA, reverse TSA, or hemiarthroplasty of the shoulder were included. Patients who underwent revision TSA were excluded. Twenty-one patients received ISNBs and 37 received liposomal bupivacaine injections. This study was approved by our Institutional Review Board.

Baseline data for each patient were age, sex, body mass index, and the American Society of Anesthesiologists (ASA) Physical Status Classification. The primary outcome measure was the numeric rating scale (NRS) pain score at 4 postoperative time intervals. The NRS pain score has a range of 0 to 10, with 10 representing severe pain. Data were gathered from nursing and physical therapy notes in patient charts. The postoperative time intervals were 0 to 1 hour, 8 to 14 hours, 18 to 24 hours, and 27 to 36 hours. Available NRS scores for these time intervals were averaged. Patients were included if they had pain scores for at least 3 of the postoperative time intervals documented in their charts. Secondary outcome measures were LOS and opioid consumption during hospital admission. Intravenous acetaminophen use was also measured in both groups. All data on opioids were converted to oral morphine equivalents using the method described by Schneider and colleagues.⁸

A board-certified, fellowship-trained anesthesiologist, experienced in regional anesthesia, administered the single-shot ISNB before surgery. The block was administered under ultrasound guidance using a 44-mm, 22-gauge needle with the patient in the supine position. No indwelling catheter was used. The medication consisted of 30 mL of 5% ropivacaine (5 mg/mL). The surgeon injected liposomal bupivacaine (266 mg diluted into 40 mL of injectable saline) near the end of the procedure throughout the pericapsular area and multiple layers of the wound, per manufacturer guidelines.⁹ A 60-mL syringe with a 20-gauge needle was used. All operations were performed by 1 board-certified, fellowship-trained surgeon using a standard deltopectoral approach with the same surgical equipment. The same postoperative pain protocol was used for all patients, including intravenous

acetaminophen and patient-controlled analgesia. Additional oral pain medication was provided as needed for all patients. Physical therapy protocols were identical between groups.

Statistical Analysis

Mean patient ages in the 2 treatment groups were compared using the Student *t* test. Sex distribution and the ASA scores were compared using a χ^2 test and a Fisher exact test, respectively. Arthroplasty types were compared using a Fisher exact test. The medians and interquartile ranges of the NRS scores at each time point measured were tabulated by treatment group, and at each time point the difference between groups was tested using nonparametric rank sum tests.

We tested the longitudinal trajectory of NRS scores over time, accounting for repeated measurements in the same patients using linear mixed model analysis. Treatment group, time period as a categorical variable, and the interaction between treatment and time period were included as fixed effects, and patient identification number was included as the random effect. An initial omnibus test was performed for all treatment and treatment-by-time interaction effects. Subsequently, the treatment-by-time interaction was tested for each of the time periods. The association of day of discharge (as a categorical variable) with treatment was tested using the Fisher exact test. All analyses were conducted using Stata, version 13, software (StataCorp LP). *P* values <.05 were considered significant.

Sample Size Analysis

We calculated the minimum detectable effect size with 80% power at an alpha level of 0.05 for the nonparametric rank sum test in terms of the proportion of every possible pair of patients treated with the 2 treatments, where the patient treated with liposomal bupivacaine has a lower pain score than the patient treated with ISNB. For pain score at 18 to 24 hours, the sample sizes of 33 patients treated with liposomal bupivacaine and 20 treated with ISNB, the minimum detectable effect size is 73%.

Results

Fifty-eight patient charts (21 in the ISNB group and 37 in the liposomal bupivacaine group) were

The primary outcome measure, numeric rating scale (NRS) pain score, showed no significant differences between groups at 0 to 1 hour after surgery (*P* = .99) or 8 to 14 hours after surgery (*P* = .208).

reviewed for the study. Patient sex distribution, mean age, mean body mass index, and mean baseline ASA scores were not statistically different (**Table 1**). In the ISNB group, 5 patients had hemiarthroplasty, 12 had TSA, and 4 had reverse TSA. In the liposomal bupivacaine group, 1 patient had hemiarthroplasty, 23 had TSA, and 13 had reverse TSA. Frequency of procedure types was significantly different between groups ($P = .039$), with the liposomal bupivacaine group undergoing fewer hemiarthroplasties.

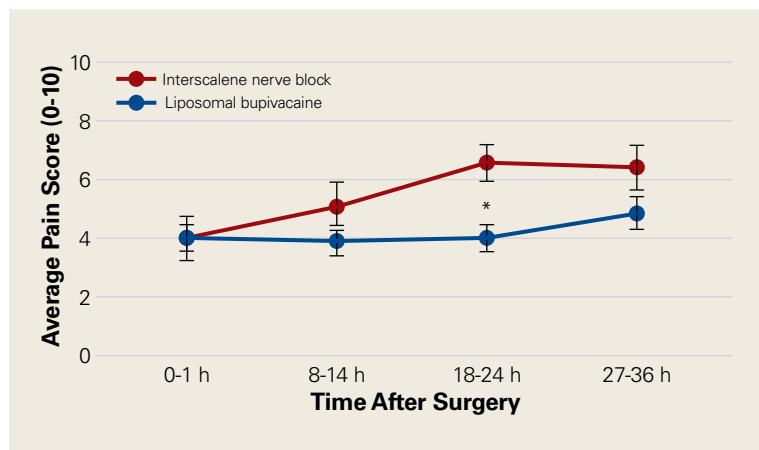


Figure 1. The means (dots) and standard errors (bars) of numeric rating scale pain scores derived from linear mixed model analysis are plotted against the median measurement time. In a combined test for all measurement periods, there was a difference in numeric rating scale score by treatment ($P = .010$). On examining every time point separately, we found that only the 18- to 24-hour period showed a statistically significant difference by treatment ($P = .013$).

*Indicates significant difference.

The primary outcome measure, NRS pain score, showed no significant differences between groups at 0 to 1 hour after surgery ($P = .99$) or 8 to 14 hours after surgery ($P = .208$). At 18 to 24 hours after surgery, the liposomal bupivacaine group had a lower mean NRS score than the ISNB group ($P = .001$). This was statistically significant when taking repeated measures of variance into account (**Figure 1**). Mean NRS score was also lower for the liposomal bupivacaine group at 27 to 36 hours after surgery ($P = .029$). This was a significant difference when repeated measures of variance was considered (**Table 2**).

There was no difference in the amount of intravenous acetaminophen given during the hospital stay between groups. There was no significant difference in opioid consumption on postoperative day 1 in the hospital ($P = .59$) (**Figure 2**).

However, there were significant differences between groups on postoperative days 2 and 3. On postoperative day 2, the ISNB group required significantly more opioids (mean, 112 mg morphine equivalents) than the liposomal bupivacaine group (mean, 37 mg morphine equivalents) ($P = .001$). The ISNB group also required significantly more opioids (mean, 25 mg morphine equivalents) on postoperative day 3 than the liposomal bupivacaine group (mean, 5 mg) ($P = .002$).

Sixteen of 37 patients in the liposomal bupivacaine group and 2 of 21 in the ISNB group were discharged on the day after surgery ($P = .010$) (**Table 3**). The mean LOS was 46 ± 20 hours for

Table 1. Characteristics of 58 Patients Who Underwent Shoulder Arthroplasty by a Single Surgeon from January 2012 to January 2015

Characteristic	Interscalene Nerve Block (N = 21)		Liposomal Bupivacaine (N = 37)		P
	Mean (SD)	No. (%)	Mean (SD)	No. (%)	
Age (y)	63 (14)		65 (12)		.524
Female sex		12 (57)		20 (54)	.830
Body mass index	28.8 (7.3)		31.8 (7.0)		.166
Procedure					
Hemiarthroplasty		5 (24)		1 (3)	.039
TSA		12 (57)		23 (62)	
Reverse TSA		4 (19)		13 (35)	
ASA level					
1		2 (9.5)		0 (0)	.206
2		9 (43)		15 (40)	
3		10 (48)		22 (59)	

Abbreviations: ASA, American Society of Anesthesiologists; TSA, total shoulder arthroplasty.

the liposomal bupivacaine group and 57 ± 14 hours for the ISNB group ($P = .012$).

There were no major cardiac or respiratory events in either group. No long-term paresthesias or neuropathies were noted. There were no readmissions for either group.

Discussion

Postoperative pain control after shoulder arthroplasty can be challenging, and several modalities have been tried in various combinations to minimize pain and decrease adverse effects of opioid medications. The most common method for pain relief after shoulder arthroplasty is the ISNB. Several studies of ISNBs have shown improved pain control after shoulder arthroplasty with associated decreased opioid consumption and related side effects.¹⁰ Patient rehabilitation and satisfaction have improved with the increasing use of peripheral nerve blocks.¹¹

Despite the well-established benefits of ISNBs, several limitations exist. Although the superior portion of the shoulder is well covered by an ISNB, the inferior portion of the brachial plexus can remain uncovered or only partially covered.¹² Complications of ISNBs include hemidiaphragmatic paresis, rebound pain 24 hours after surgery,¹³ chronic neurologic complications,¹⁴ and substantial respiratory and cardiovascular events.¹⁵ Nerve blocks also require additional time and resources in the perioperative period, including an anesthesiologist with specialized training, assistants, and ultrasonography or nerve stimulation equipment contraindicated in patients taking blood thinners.¹⁶

Periarticular injections of local anesthetics have also shown promise in reducing pain after arthroplasty.⁴ Benefits include an enhanced safety profile

because local injection avoids the concurrent blockade of the phrenic nerve and recurrent laryngeal nerve and has not been associated with the risk of peripheral neuropathies. Further, local injection is a simple technique that can be performed during surgery without additional personnel or expertise. A limitation of this approach is the relatively short duration of effectiveness of the local anesthetic and uncertainty regarding the best agent and the ideal volume of injection.⁶ Liposomal bupivacaine is a new agent (approved by the US Food and Drug Administration in 2011¹⁷) with a sustained release over 72 to 96 hours.¹⁸ The most common adverse effects of liposomal bupivacaine are nausea, vomiting, constipation, pyrexia, dizziness, and headache.¹⁹ Chondrotoxicity and granulomatous inflammation are more serious, yet rare, complica-

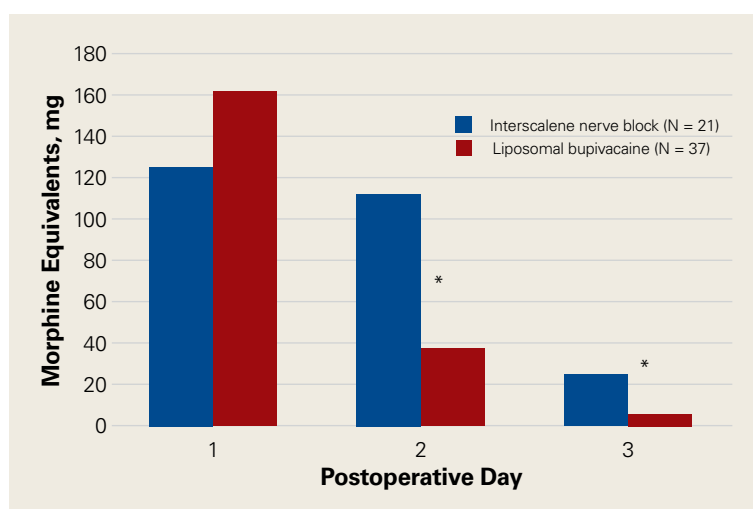


Figure 2. Comparison of mean opioid use for patients treated with interscalene nerve block and liposomal bupivacaine after shoulder arthroplasty. *Indicates significant difference (day 2: $P = .001$; day 3: $P = .002$).

Table 2. Pain Scores of 58 Patients After Shoulder Arthroplasty^a

Time After Surgery	Interscalene Nerve Block (N = 21)		Liposomal Bupivacaine (N = 37)		P ^b
	Pain Score ^c	No. ^d	Pain Score ^c	No. ^d	
0 to 1 h	3 (0, 7)	13	4 (0, 8)	37	.990
8 to 14 h	5.5 (4, 7)	10	4 (3, 6)	27	.208
18 to 24 h	6.5 (5, 8)	20	4 (2, 6)	33	.001
27 to 36 h	7 (5, 7.5)	12	5 (4, 6)	22	.029
10 d	4.5 (2.25, 6.5)	12	2 (1, 3)	35	.094

^aPain scores based on numeric rating scale (range 0 to 10, with 10 representing severe pain).

^bP-value from rank sum test.

^cData presented as the median (25th, 75th percentile).

^dNumber of patients assessed at time point.

tions of liposomal bupivacaine.²⁰

We found that liposomal bupivacaine injections were associated with lower pain scores compared with ISNB at 18 to 24 hours after surgery. This correlated with less opioid consumption in the liposomal bupivacaine group than in the ISNB group on the second postoperative day. These differences in pain values are consistent with the known pharmacokinetics of liposomal bupivacaine.¹⁸ Peak plasma levels normally occur approximately 24 hours after injection, leaving the early postoperative period

relatively uncovered by anesthetic agent. This finding of relatively poor pain control early after surgery has also been noted in patients undergoing knee arthroplasty.⁵ On the basis of the findings of this study, we have added standard bupivacaine injections to our separate liposomal bupivacaine injection to cover early postoperative pain. Opioid consumption was significantly lower in the liposomal bupivacaine group than in the ISNB group on postoperative days 2 and 3. We did not measure adverse events relat-

ed to opioid consumption, so we cannot comment on whether the decreased opioid consumption was associated with the rate of adverse events. However, other studies^{21,22} have established this relationship.

We found the liposomal bupivacaine group to have earlier discharges to home. Sixteen of 37 patients in the liposomal bupivacaine group compared with 2 of 21 patients in the ISNB group were discharged on the day after surgery. A mean reduction in LOS of 18 hours for the liposomal bupivacaine group was statistically significant ($P = .012$). This reduction in LOS has important implications for hospitals and value analysis commit-

tees considering whether to keep a new, more expensive local anesthetic on formulary. Savings from reduced LOS and improvements in patient satisfaction may justify the expense (approximately \$300 per 266-mg vial) of Exparel.

From a societal cost perspective, liposomal bupivacaine is more economical compared with ISNB, which adds approximately \$1500 to the cost of anesthesia per patient.²³ Eliminating the costs associated with ISNB administration in shoulder arthroplasties could result in substantial savings to our healthcare system. More research examining time savings and exact costs of each procedure is needed to determine the true cost effectiveness of each approach.

Limitations of our study include the retrospective design, relatively small numbers of patients in each group, missing data for some patients at various time points, variation in the types of procedures in each group, and lack of long-term outcome measures. It is important to note that we did not confirm the success of the nerve block after administration. However, this study reflects the effectiveness of each of the modalities in actual clinical conditions (as opposed to a controlled experimental setting). The actual effectiveness of a nerve block varies, even when performed by an experienced anesthesiologist with ultrasound guidance. Furthermore, immediate postoperative pain scores in the nerve block group are consistent with those of prior research reporting pain values ranging from 4 to 5 and a mean duration of effect ranging from 9 to 14 hours.^{23,24} Additionally, the patients, surgeon, and nursing team were not blinded to the treatment group. Although we did note a significant difference in the types of procedures between groups, this finding is related to the greater number of hemiarthroplasties performed in the ISNB group ($N = 5$) compared with the liposomal group ($N = 1$). Because of this variation

Our results suggest that liposomal bupivacaine may provide superior or similar pain relief compared with interscalene nerve block (ISNB) after shoulder arthroplasty.

Table 3. Day of Discharge After Shoulder Arthroplasty Comparing 58 Patients Treated by Interscalene Nerve Block vs Liposomal Bupivacaine

Day of Discharge After Surgery ^a	Interscalene Nerve Block (N = 21)	Liposomal Bupivacaine (N = 37)
1	2	16
2	15	19
3	2	2
4	2	0

^aSignificant difference between treatment groups from Fisher exact test ($P = .010$).

and the decreased invasiveness of hemiarthroplasties, the bias is against the liposomal group. Finally, our primary outcome variable was pain, which is a subjective, self-reported measure. However, our opioid consumption data and LOS data corroborate the improved pain scores in the liposomal bupivacaine group.

Limiting the study to a single surgeon may limit external validity. Another limitation is the lack of data on adverse events related to opioid medication use. There was no additional experimental group to determine whether less expensive local anesthetics injected locally would perform similarly to liposomal bupivacaine. In total knee arthroplasty, periarticular injections of liposomal bupivacaine were not as effective as less expensive periarticular injections.²⁵ It is unclear which agents (and in what doses or combinations) should be used for periarticular injections. Finally, we acknowledge that our retrospective study design cannot account for all potential factors affecting discharge time.

This is the first comparative study of liposomal bupivacaine and ISNB in TSA. The study design allowed us to control for variables such as surgical technique, postoperative protocols (including use and type of sling), and use of other pain modalities such as patient-controlled analgesia and intravenous acetaminophen that are likely to affect postoperative pain and LOS. This study provides preliminary data that confirm relative equipoise between liposomal bupivacaine and ISNB, which is needed for the ethical conduct of a randomized controlled trial. Such a trial would allow for a more robust comparison, and this retrospective study provides appropriate pilot data on which to base this design and the clinical information needed to counsel patients during enrollment.

Our results suggest that liposomal bupivacaine may provide superior or similar pain relief compared with ISNB after shoulder arthroplasty. Additionally, the use of liposomal bupivacaine was associated with decreased opioid consumption and earlier discharge to home compared with ISNB. These findings have important implications for pain control after TSA because pain represents a major concern for patients and providers after surgery. In addition to clinical improvements, use of liposomal bupivacaine may save time and eliminate costs associated with administering nerve blocks. Local injection may also be used in patients who are contraindicated for ISNB such as those with obesity, pulmonary disease, or peripheral neuropathy. Although we cannot definitively suggest that

liposomal bupivacaine is superior to the current gold standard ISNB for pain control after shoulder arthroplasty, our results suggest a relative clinical equipoise between these modalities. Larger analytical studies, including randomized trials, should be performed to explore the potential benefits of liposomal bupivacaine injections for pain control after shoulder arthroplasty.

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