Efficacy of Liposomal Bupivacaine versus Ropivacaine in Adductor Canal Block for Total Knee Arthroplasty

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Abstract

Adductor canal block (ACB) is advantageous for postoperative analgesia in total knee arthroplasty (TKA) because it results in minimal motor block. Liposomal bupivacaine (LB) is Food and Drug Administration-approved extended-release formulation of bupivacaine for interscalene peripheral nerve blocks. Its use is increasing in the TKA setting, mainly as a local infiltration agent. We compared the efficacy of ACB using LB versus ropivacaine in TKA. Two cohorts of patients were retrospectively analyzed at a single institution receiving ropivacaine and LB ACB for TKA. Duration of LB ACB, time to first opioid use postrecovery room, amount of opioid use postrecovery room, length of stay (LOS), and average and highest pain scores were collected. A total of 91 and 142 TKA patients received ropivacaine and LB for ACB, respectively. At 8 hours postrecovery room, more patients in the LB group required no opioids compared with the ropivacaine group ($p = 0.026$). Mean opioid consumption was lower in the LB group than in the ropivacaine group at 8 and 24 hours postrecovery room, although statistical significance was only observed at 8 hours ($p = 0.022$). The highest pain score for patients in the two groups was not statistically different. The average pain score for patients with a 2-day LOS was higher in the LB group, but average pain scores were similar for patients with 1- and 3-day LOS. Median LOS for the LB and ropivacaine groups was 1 and 2 days, respectively ($p < 0.0001$). Significantly lower opioid use at 8 hours postrecovery room was seen in the LB group compared with the ropivacaine group. There was no difference in opioid use at 24 and 48 hours. There was also no advantage with LB ACB in decreasing pain scores. However, the LB ACB group demonstrated a significantly shorter LOS compared with the ropivacaine ACB group.

Keywords

- liposomal bupivacaine
- adductor canal block
- total knee arthroplasty

Total knee arthroplasty (TKA) is an effective procedure for the treatment of osteoarthritis, offering benefits of pain relief, increased mobility, and improved quality of life. A challenge in postoperative care is achieving adequate pain control. Suboptimal pain management may result in prolonged use of opioid medications, increased nausea and vomiting, delayed ambulation leading to rising deep venous thrombosis risk, and increased hospital stay.

Adductor canal block (ACB) is an accepted technique for selectively anesthetizing predominantly the saphenous nerve and posterior branch of the obturator nerve distributions to provide anesthesia to the anterior and medial knee.[1]

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The volume of local anesthetic used commonly ranges between 10 and 30 mL.[2,3] The benefit of ACB in comparison with femoral nerve block is that ACB results in less compromised quadriceps muscle strength, which is important for postoperative rehabilitation and minimizing fall risk.[4–6] Periarticular infiltration provides analgesia to portions of the knee not covered by ACB.

Currently, bupivacaine and ropivacaine are commonly used medications in ACB.[1,6–8] The duration of analgesia for ropivacaine lasts between 7 and 15 hours.[9] Ropivacaine and bupivacaine have similar analgesic effect when used for peripheral nerve blocks.[10] Adjunct medications added to peripheral nerve blocks to augment duration of action such as epinephrine,[1,5] buprenorphine,[11] clonidine,[12–14] dexmedetomidine,[15] and dexamethasone[16,17] yielded unsatisfactory or conflicting results, with some carrying additional side effects such as increased nausea, vomiting, bradycardia, and hypotension.

Liposomal bupivacaine (LB) is a multivesicular liposomal formation of bupivacaine that facilitates its extended release, resulting in prolonged analgesic effect.[18] In 2011, LB was approved for local infiltration following two large phase III randomized control trials for use in hemorrhoidectomy and bunionectomy.[19–21] When administered as a local infiltration for TKA, LB was shown to decrease opioid use in the first 24 hours.[22] Local infiltration using LB in conjunction with ACB resulted in lower pain scores at 36 hours post TKA compared with ropivacaine pain ball.[23] Periarticular injection of LB-containing solution in combination with ACB reduced postoperative opioid use and improved sit-to-stand measures compared with non-LB and femoral nerve block.[24] However, there are contrasting studies that demonstrate periarticular infiltration of LB does not offer any advantage in pain control or functional recovery to that of bupivacaine alone.[25]

In animal studies, high-dose perineural LB injection was not observed to cause nerve damage.[26] Pacira pharmaceuticals conducted two large studies using LB for femoral nerve blocks with safety profile similar to placebo, except more falls were reported for patients in the LB group.[27] Unfortunately, Pacira did not include femoral nerve block using ropivacaine or bupivacaine alone to compare the fall risk as opposed to LB. Safety and efficacy of LB for interscalene brachial plexus nerve block was also performed which resulted in a Food and Drug Administration (FDA)-approval of LB for interscalene brachial plexus nerve block. More recently, Lakra et al showed no adverse events when LB was added to ACB.[28]

The purpose of this retrospective study was to investigate the use of LB in ACB by comparing the efficacy of LB and bupivacaine ACB solution against ropivacaine ACB. Our hypothesis was that ACB containing LB would lead to increased duration of analgesia, reduced opioid use, increased time to first opioid rescue, and decreased LOS.

Methods

This study was approved by our institutional review board (IRB 2018000288). The ropivacaine ACB cohort underwent TKA from April to May 2017, and the LB ACB cohort underwent TKA from late-October 2017 to mid-February 2018. Patients who received ropivacaine only will be categorized as the ropivacaine group and those who received LB with bupivacaine will be categorized as the LB group. Patients did not receive ACB if they declined the procedure following informed consent discussion or if there were contraindications including history of allergy to local anesthetic, local skin infection, and body habitus precluding delivery of anesthetic to the adductor canal target with a 100-mm needle. Chronic pain patients were not explicitly sought nor excluded from the study. Of those who received ACB, cases with incomplete charting were excluded from analysis.

All ACB were performed in the operating room under ultrasound guidance with a Sonosite 15–6 MHz linear probe by the assigned anesthesiologist for the case. The femoral artery running underneath the sartorius muscle was identified by placing the transducer over the mid-thigh, and using either an 80-mm or 100-mm needle, local anesthetic was injected adjacent to the artery and deep to the sartorius fascia in the vicinity of the saphenous nerve, similar to the method previously described.[29] In the ropivacaine group, ACB solution consisted an average of 20 mL of 0.5% ropivacaine. In the LB group, ACB solution consisted of 10 mL of LB with an average of 12 mL of 0.25% bupivacaine. The volume of local anesthetic was administered at the discretion of individual anesthesiologists.

Either general or spinal anesthesia was given intraoperatively depending on patient's preference. There were 11 anesthesiologists participating in this study. All surgical cases were performed by one surgeon with over 20 years of knee arthroplasty experience. Patients received 650 mg acetaminophen and 40 mg pantoprazole PO preoperatively. Intraoperatively, patients received 4 mg dexamethasone and up to 30 mg ketorolac IV depending on renal function.

In both the ropivacaine and LB groups, local infiltration and intra-articular injection were performed by the surgeon. In the ropivacaine group, a mixture of 20 mL (266 mg) of LB and 60 mL of saline was administered. In the LB group, a mixture of 10 mL (133 mg) of LB and 70 mL of saline was administered. In both groups 20 mL of 0.25% bupivacaine with 1:200,000 epinephrine was injected subcutaneously. Postoperatively following their stay in the recovery room, patients received Ketorolac every 6 hours for 24 hours unless there was a contraindication to the medication. Opioid medications were available on an as-needed basis.

Data collection included time-to-first opioid use postrecovery room and total amount of narcotics used, expressed in morphine equivalent dose (MED) in milligrams, at 8, 24, and 48 hours postrecovery room. The average and highest pain scores with activities were based on a scale of 0 to 10 with 10 being the worst pain ever experienced. A pain score of 1 to 3 was documented as mild pain. Duration of ACB in the LB group was determined from the time of placement to the time that the patient reported more than mild pain in the medial or anterior knee, which was organized into three time blocks: 0 to 8, 8 to 16, and 16 hours or longer postrecovery room.

The length of stay (LOS) was based on the number of days the patient was in the hospital with partial days rounded up to the full day. Ropivacaine group patients were required to stay at least 1 day per surgical protocol at the time this portion of the study was conducted, and following the ropivacaine cohort, the protocol subsequently permitted same-day discharge of TKA patients. All patients in the LB group who were discharged on the day of the surgery were upgraded to a 1-day LOS for analysis purpose.

Data were charted by nurses in the epic electronic medical record and collated by the pain management team pharmacist. Physical therapy started on the first postoperative day, twice per day. Discharge criteria included adequate pain control on oral pain medication, independent transfer, ambulation of at least 200 feet, and the ability to climb stairs if the patient had stairs at home. Postoperative adverse events were documented by either the nurse or the physical therapist.

Statistical Analysis

The Kolmogorov–Smirnov test was used to determine if the amount of opioid consumption, pain scores, and LOS followed a Gaussian curve. Differences in demographics between the ropivacaine and the LB groups were assessed with the Chi-square test. Binary logistic regression was applied to compare incidence of opioid use between the ropivacaine and LB groups at 8, 24, and 48 hours after controlling for the type of anesthesia. The ANCOVA test was used to calculate for statistical significance in the amount of opioid consumption, average and highest pain scores, and LOS with the type of anesthesia set as the covariate. Quantification of opioid consumption in MED was logarithmically transformed for analysis purpose.

Statistical significance was set at a p-value of less than 0.05 with a two-tailed hypothesis testing. Medcalc was used to perform the two-sample t-test between proportions. IBM SPSS Statistics version 25.0.0 was used to perform Kolmogorov–Smirnov test, binary logistic regression, and ANCOVA.

Results

From April to May 2017, 104 TKAs were performed with ropivacaine ACB; 13 were excluded from analysis, leaving 91 cases in the ropivacaine study group. From late-October 2017 to mid-February 2018, 181 TKAs were performed with LB ACB; 39 were excluded, leaving 142 patients in the LB study group. ►**Table 1** compares the number of patients, gender, age, ASA classification, and type of anesthesia between the ropivacaine and LB groups. A statistically higher percentage of patients elected to receive general anesthesia in the ropivacaine group compared with the LB group.

Duration of ACB effect in the LB group is presented in ►**Fig. 1**. A total of 18 and 46% of patients did not report any anterior or medial knee pain between 8 and 16 hours and until after 16 hours, respectively. Of the patients who did not experience anterior or medial knee pain until after 16 hours, 73% reported no pain for at least 24 hours.

In the first 8 hours after recovery room, 12% more patients in the LB group did not use opioids as compared with the ropivacaine group ($p = 0.026$). There was no significant difference in the percentage of patients requesting opioids at 24 hours. All patients in both groups who stayed in the hospital for more than one day required opioids by 48 hours (►**Table 2**).

Opioid consumption for the ropivacaine and LB groups is presented in ►**Table 3**. At 8 hours, quantity of opioid use in the LB group was statistically lower than that of the ropivacaine group ($p = 0.022$). Although there was a reduction in the mean and median opioid use at 24 hours for the LB group as compared with the ropivacaine group (53 and 47 MED vs. 50 and 45 MED, respectively), the result did not reach statistical significance.

The highest pain score for the ropivacaine and LB groups was not statistically different among patients with LOS of 1, 2, and 3 days. The average pain score was similar for the ropivacaine and LB groups among patients with LOS of 1 and 3 days. However, among patients with LOS of 2 days, patients in the ropivacaine group had lower average pain scores compared with those in the LB group (median 4.3 vs. 5.0, $p = 0.009$; ►**Table 4**).

►**Fig. 2** shows LOS for the ropivacaine and LB groups, expressed as percentage of their total respective cohorts. Three same-day discharge patients in the LB group were rounded up to a 1-day LOS. Median LOS was shorter in the LB

Table 1 Demographics

		Ropivacaine $n = 91$	LB $n = 142$	p-Value
Age (y) mean ± standard deviation		69 ± 9	70 ± 8	
Gender (%)	Female	57 (63)	87 (61)	0.760
	Male	34 (37)	55 (39)	0.760
ASA classification (%)	1	6 (7)	10 (7)	1.000
	2	51 (56)	84 (59)	0.652
	3	34 (37)	48 (34)	0.641
Type of anesthesia (%)	General	59 (65)	71 (50)	0.025
	Spinal	32 (35)	71 (50)	0.025

Abbreviations: ASA, adductor canal block; LB, liposomal bupivacaine; n, number of patients.

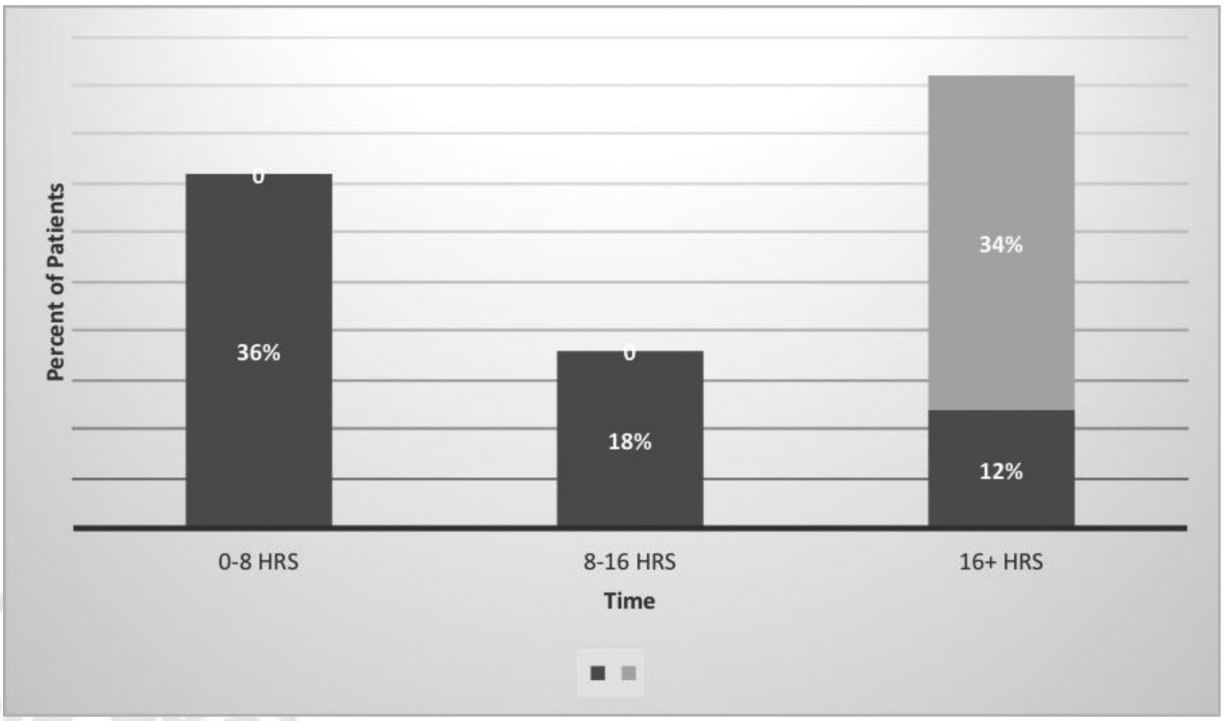

Fig. 1 Duration of adductor canal block with liposomal bupivacaine. Lighter gray = adductor canal block lasting 24 hours or longer.

group compared with the ropivacaine group (1 vs. 2 days, $p < 0.0001$).

One adverse event, a nonocclusive deep venous thrombosis, was reported in the LB group and no adverse event was reported in the ropivacaine group. No patients experienced signs of local toxicity or falls.

Discussion

Multiple studies have examined the efficacy of LB in TKA, but the preponderance of data is in the setting of local infiltration. A retrospective study that reviewed billing data for approximately 89,000 TKA cases found that LB did not decrease opioid prescription or complication.[30] In 2016, a study using 266 mg of LB in femoral nerve blocks yielded modestly lower pain scores and opioid requirements.[31] There is still a paucity of data addressing outcomes of LB administered for ACB. Lakra et al showed that there is improved pain control with LB in ACB and periarticular injection as opposed to that of bupivacaine alone in ACB and periarticular injection.[28] Unfortunately, their results do not differentiate the effect of LB in the periarticular infiltration versus that of the ACB. Our study examines the efficacy of LB for use in ACB, where it is commonly used for postoperative pain control after TKA as it predominantly blocks sensory over motor.

Comparison analysis between the ropivacaine and LB groups was performed retrospectively, but the data were collected prospectively by the institution's pain pharmacist. Prior to switching from ropivacaine ACB to LB ACB, patients in the ropivacaine group were not asked to localize postoperative knee pain. Data regarding pain in the anterior and medial aspects of the knee, the expected anesthetic distribution of ACB, was unavailable and constituted a limitation regarding the exact assessment of ropivacaine ACB duration.

The 8 hours for our approximate duration of the ropivacaine group is consistent with Fanelli's review paper that reported the ropivacaine analgesic duration lasting anywhere between 7 and 15 hours for peripheral nerve blocks.[9]

Table 2 Percentages of patients requiring no opioids at specific time frames postrecovery room

	Ropivacaine ACB $n = 91$	LB + bupivacaine ACB $n = 142$	*p*-Value
No opioid used within the first 8 hours	21%	33%	0.026
No opioid used within the first 24 hours	5%	6%	0.915
No opioid used within the first 48 hours	0%	0%	1.000

Abbreviations: ACB, adductor canal block; *n*, number of patients.

Table 3 Opioid Consumption in morphine equivalent dosing

		Ropivacaine ACB in MED (*n*)	LB + bupivacaine ACB in MED (*n*)	*p*-Value
8 hours post-RR	Mean	16 ± 17 (14–18)	11 ± 11 (9–13)	0.022
	Median	10	10	
	IQR	15	13.75	
	Range	0–100	0–50	
	Number of patients	91	142	
24 hours post-RR	Mean	53 ± 36 (47–59)	47 ± 31 (41–53)	0.190
	Median	50	45	
	IQR	40	50	
	Range	0–189	0–142.5	
	Number of patients	91	142	
48 hours post-RR	Mean	120 ± 87 (102–138)	113 ± 49 (101–125)	0.877
	Median	105	114	
	IQR	99	70	
	Range	10–458	15–232.5	
	Number of patients	64	69	

Abbreviations: ACB, adductor canal block; IQR, interquartile range; LB, liposomal bupivacaine; MED, morphine equivalent dosing; *n*, number of patients; RR, recovery room; ( ), confidence interval at 95% confidence level.

Table 4 Average and highest pain scores with activities for ropivacaine and liposomal bupivacaine groups based on patient's length of stay

LOS in days	Pain score type	Ropivacaine group pain score expressed as median (IQR)	LB group pain score expressed as median (IQR)	*p*-Value
1		*n* = 18	*n* = 71	
	Average	3.1 (2.2)	3.8 (1.7)	0.374
	Highest	5.0 (3.0)	5.0 (3.0)	0.863
2		*n* = 38	*n* = 55	
	Average	4.3 (2.2)	5.0 (2.1)	0.009
	Highest	6.0 (3.0)	7.0 (2.0)	0.077
3		*n* = 20	*n* = 14	
	Average	5.0 (2.4)	5.5 (2.4)	0.433
	Highest	7.0 (2.8)	8.0 (2.8)	0.494

Abbreviations: IQR, interquartile range; LB, liposomal bupivacaine; LOS, length of stay; *n*, number of patients.

Therefore, the low and high ends of that range were used as cut off points when LB duration was analyzed. Pain relief at the anterior and medial aspect of the knee lasting less than 8 hours suggested failure of LB or the ACB to provide adequate analgesia, whereas pain relief at the anterior and medial knee lasting greater than 16 hours suggested prolonged analgesic effect from LB. Pain relief between 8 and 16 hours was indeterminant for LB efficacy. Lack of analgesic effect for more than 8 hours may have resulted from technically suboptimal block placement, patient mislocalization of postoperative pain to the anterior and/or medial knee, or charting errors.

A comparison of the ropivacaine and the LB group demographics showed that the type of anesthesia may be a confounding factor when analyzing the data, as more patients received general anesthesia in the ropivacaine group. We therefore used the statistical test ANCOVA to account for this difference when analyzing the amount of opioid use, pain score, and the LOS. Only the data for the amount of opioid use were logarithmically transformed to model a Gaussian distribution as the ANCOVA is the preferred test in randomized trials except in extreme cases of non-normally distributed data where the Mann–Whitney U test may be more reliable.[32]

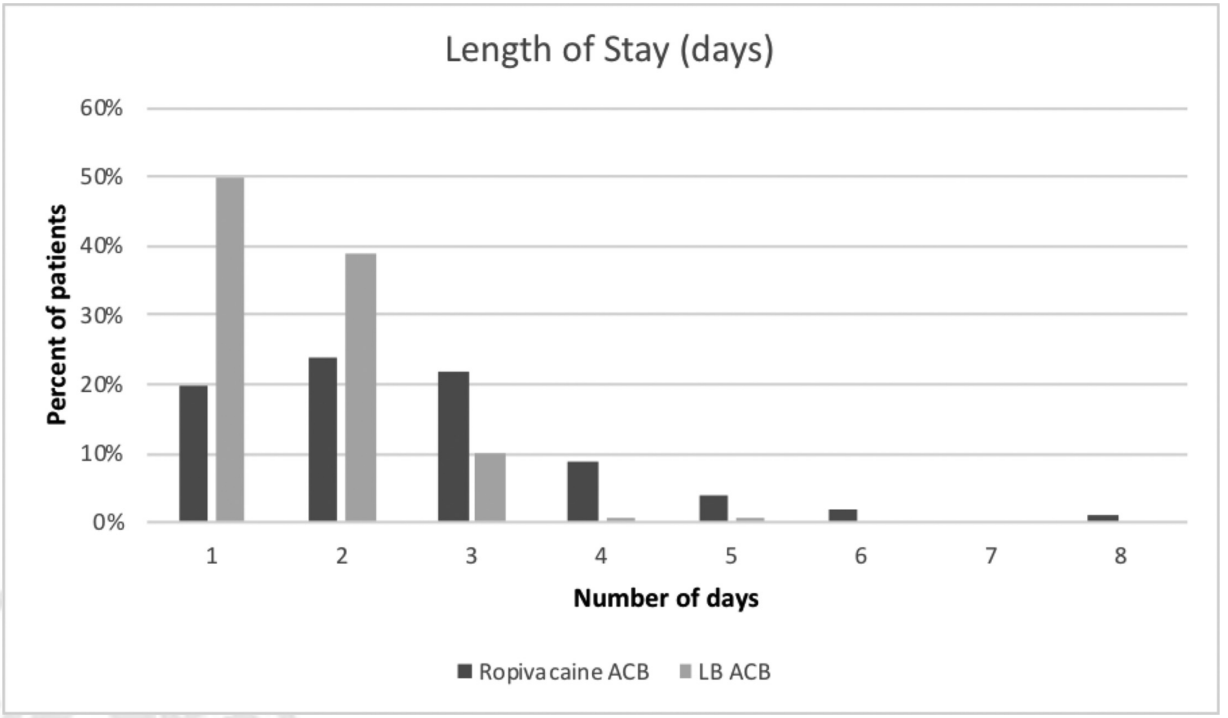

Fig. 2 Length of stay.

The percentage of patients requiring no opioids and the amount of opioid use within 8 hours was significantly lower in the LB group compared with the ropivacaine group. At 48 hours, the median dosage of opioid in the LB group was higher than in the ropivacaine group; however, the difference was not statistically significant. The finding at 48 hours was not surprising, as by this time we would expect most of the ACB to have worn off leaving patients to rely on opioids for pain control.

The lack of statistical significance at 24 hours was somewhat unexpected, as LB duration has been shown to last between 24 and 48 hours.[33] In our study, the location of pain prompting opioid use was not recorded, and opioid administration for pain in locations other than the anterior or medial knee would not be supportive of LB ACB failure. The lack of statistical significance at 24 hours may also result from differences in intra-articular administration of LB between the LB and ropivacaine groups. In the ropivacaine cohort the entire vial of LB (266 mg of LB) was used for intra-articular injection, while this dose was split evenly for intra-articular injection (133 mg of LB) and ACB (133 mg of LB) in the LB group. Therefore, in the 24 hours postrecovery room, some patients in the LB group may have required earlier administration of opioids—presumably for pain in the posterior and lateral knee covered by intra-articular injection—than they otherwise would have needed if they received an identical dose of intra-articular LB as the ropivacaine group.

We found that the highest and average pain scores for the ropivacaine and LB groups were similar for patients with LOS of 1 and 3 days. This was also true for the highest pain score for LOS of 2 days. The exception was that patients with LOS of 2 days had lower average pain scores in the ropivacaine group compared with the LB group. This may reflect the differential opioid administration between the two groups as the ropivacaine group received more opioids at 8 and 24 hours, thus possibly lowering the pain score. At 48 hours, there was no difference in opioid dose between the ropivacaine and LB groups, suggesting that similar average pain scores in patients with LOS of 3 days may, in part, be attributable to a parity in narcotics administration later in hospitalization. Another explanation for the similar pain scales between the ropivacaine and the LB group and the increase pain in the LB group at 48 hours may be that patients in the LB group have been more active since they experienced less pain initially, but increased activity have paradoxically precipitated greater delayed pain. Moreover, the timing and amount of narcotic administration may confound the reporting of pain scores.

This study did not show that LB ACB significantly decreased pain score and opioid consumption at the expected time frame of 24 to 48 hours. Potential type 2 error must be acknowledged for pain scores at LOS 1 and 3 and MED at 24 and 48 hours. Calculated effect size at 24 and 48 hours was small with a clear clinical difference in MED between the two groups. Notably, however, when using objective discharge criteria as described in methods, there was a significantly decreased LOS for the LB group compared with the ropivacaine group ($p < 0.0001$). Patients in the LB group may have demonstrated better functional status allowing for earlier discharge. The meta-analysis by Singh et al reported decreased LOS with LB periarticular infiltration,[34] however, LB in ACB demonstrated a more profound decrease in LOS. Cost savings and improved patient satisfaction associated with an earlier discharge are potential benefits of LB ACB.

Prospective studies comparing ropivacaine and LB in a larger sample size are needed to further evaluate the efficacy

of LB in ACB. Such studies should control for the total amount of LB used for local infiltration. Finally, it may be worthwhile to evaluate LB versus ropivacaine for partial medial knee arthroplasty as ACB does not cover the lateral part of the knee.

Conflict of Interest
None declared.

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