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# Adductor Canal Block vs Liposomal Bupivacaine Periarticular Injection in Total Knee Arthroplasty: A Randomized Controlled Trial

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ABSTRACT

*Background:* This study compares postoperative pain scores and functional outcomes between liposomal bupivacaine peri-articular injection (LB-PAI) vs a single-shot adductor canal block (ACB) using bupivacaine HCl in patients undergoing primary total knee arthroplasty (TKA).

*Methods:* This is a randomized controlled trial of 56 patients who were treated with TKA for arthritis. Patients were randomized to receive an intraoperative LB-PAI (n = 27) or preoperative ACB using bupivacaine HCl (n = 29). Both groups were otherwise given our institutional standard multimodal pain protocol. Data on Visual Analog Scale (VAS) pain scores, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, knee range of motion, postoperative ambulation distance, hospital length of stay, and opioid use were collected. The total cost of each intervention was compared at the conclusion of the study.

*Results:* Age, gender, or body mass index was similar between groups. Compared to the ACB group, the LB-PAI group trended to lower average VAS pain scores on postoperative days 0, 1, and 2 (average difference [95% confidence interval] = −0.5 [−0.7, 1.7], −1.0 [−0.1, 2.0], −0.2 [−0.8, 1.3]), and identical average VAS pain scores on postoperative days 4 and 7. These differences and all postoperative outcome measures were not statistically significant at any time point. A single 266-milligram vial of liposomal bupivacaine costs $351, and a single-shot ACB costs $893 at our institution.

*Conclusions:* This randomized controlled trial shows similar postoperative pain control, functional outcomes, and opioid use between LB-PAI and a single-shot ACB in patients undergoing primary TKA. However, the single-shot ACB costs $542 more than the LB-PAI at our institution.



## Introduction

The number of total knee arthroplasty (TKA) procedures performed in the United States annually is projected to increase to 3.48 million by 2030 [1]. Perioperative pain management plays a significant role in a TKA patient's successful recovery. Various analgesic strategies have been implemented to help patients achieve mobility as soon as possible after surgery, in an effort to decrease cardiopulmonary complications, improve gastrointestinal function, and lower the risk of venous thromboembolism [2–4]. Multimodal pain management strategies such as spinal anesthesia, preoperative peripheral nerve blocks, oral analgesics, and periarticular injections (PAI) with opiate analgesics and anti-inflammatory medications have been considered for perioperative pain control [5,6].

Liposomal bupivacaine (EXPAREL; Pacira BioSciences, Inc., Parsippany, NJ) is an alternative perioperative analgesia method that can be delivered as a PAI [7]. Liposomal bupivacaine is approved by the United States Food and Drug Administration for surgical site infiltration to reduce postoperative pain [8,9]. The liposomal vehicle acts to slowly release the local anesthetic, leading to prolonged analgesia for a duration of approximately 72 hours [6,7,9,10]. Liposomal bupivacaine PAI (LB-PAI) in TKA has been compared with traditional local anesthetic PAI, and the results are conflicting. There are studies supporting its use [10–14] while other studies do not [15,16]. LB-PAI has also been compared with femoral nerve block (FNB) in primary TKA, and recent studies have shown improved pain scores, earlier time to ambulation, decreased need

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for breakthrough pain medications, decreased opioid consumption, decreased length of stay (LOS), and institutional cost savings with the use of liposomal bupivacaine [17–21].

Although FNB is widely used in arthroplasty, adductor canal block (ACB) has been shown to be equally efficacious without the associated complication of quadriceps muscle weakness [22,23]. ACB is currently the preferred peripheral nerve block method for TKA at our institution for this reason. To our knowledge, there has been no study directly comparing the efficacy of LB-PAI to that of ACB in TKA. The purpose of this study is to evaluate the clinical outcomes of LB-PAI when compared with single-shot ACB using bupivacaine HCl in patients undergoing a TKA. The primary outcome of interest is postoperative pain, which is measured using a Visual Analog Scale (VAS) to record ordinal pain scores on a scale from 0 to 10. Secondary measures include the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, knee range of motion, postoperative ambulation distance, hospital LOS, and opioid use.

## Methods

This is a randomized controlled trial of 57 patients with 60 TKA procedures performed by a single fellowship-trained adult reconstruction orthopedic surgeon at a community-based teaching hospital. After obtaining approval from the institutional review board, patient recruitment was conducted from March 2017 to March 2018 at the surgeon's clinic. Study participants were either self-referred or referred from community care providers for management of end-stage osteoarthritis or rheumatoid arthritis. Patients were eligible for inclusion if they were over 18 years old, undergoing a unilateral primary TKA for end-stage osteoarthritis or rheumatoid arthritis, and otherwise able to provide informed consent. Patients were excluded if they were undergoing a bilateral TKA, allergic to amide anesthetics, unable to receive intravenous tranexamic acid, weighed less than 66 kilograms, did not successfully receive a spinal anesthetic, were pregnant or breast-feeding, or were considered opioid dependent (on long-acting narcotics or taking more than 60 milligrams of morphine equivalents daily, per the Veteran Affairs definition of opioid dependency) [24].

Patients who consented to participate in the study were randomized into one of the 2 study arms. Randomization was performed using a computer-generated algorithm, which randomly ordered the numbers 1 to 60 into a list. Patients were assigned a number from this list, based on the order in which they consented to participate. Patients who were assigned numbers 1 through 30 received an LB-PAI, and patients who were assigned numbers 31 through 60 received an ACB.

ACB group received the following interventions:

1) Preoperative ACB using 15 mL of 0.5% bupivacaine HCl (no other additives, no epinephrine)
2) Preoperative spinal block with 10-15 mg of bupivacaine HCl
3) Intraoperative PAI of the following mixture:
   a) 30 mL of 0.25% bupivacaine HCl without epinephrine
   b) 5 mg morphine = 10 mL
   c) 15 mg ketorolac = 0.5 mL
   d) 80 mL of normal saline

LB-PAI group received the following interventions:

1) Intraoperative PAI of 20 mL of 266 mg of liposomal bupivacaine and 40 mL of normal saline in one syringe
2) Preoperative spinal block with 10-15 mg of bupivacaine HCl
3) Intraoperative PAI of the following mixture in a second syringe:
   a) 30 mL of 0.25% bupivacaine HCl without epinephrine
   b) 5 mg morphine = 10 mL
   c) 15 mg ketorolac = 0.5 mL
   d) 80 mL of normal saline

Patients randomized into the ACB group received a preoperative ultrasound-guided ACB using 15 mL of 0.5% bupivacaine HCl, which was performed by the anesthesiologist. Patients randomized into the LB-PAI group received an intraoperative PAI of 266 mg of LB-PAI. For patients in the LB-PAI group, a 20-mL solution of 266 mg of liposomal bupivacaine was mixed with 40 mL of normal saline, which was then infiltrated consistently in the posterior capsule, medial and lateral side of the arthrotomy, patella tendon, quadriceps tendon, quadriceps musculature, and subcutaneous soft tissue. Patients in both groups participated in the same multimodal pain control protocol consisting of pre-emptive oral pain medications, a spinal anesthetic, and a standard intraoperative PAI with bupivacaine HCl, ketorolac, and morphine. Patients in both groups underwent the same postoperative physical and occupational therapy protocol.

Patient age, sex, and body mass index (BMI) were collected at baseline from the electronic medical record. The primary outcome of interest was postoperative pain, which was measured using a VAS to record pain scores as an ordinal measure from 0 to 10 with 0 representing no pain, 5 representing moderate pain, and 10 representing worst pain. VAS pain scores were recorded before surgery and on postoperative day (POD) zero (6-8 hours after surgery), one (20-28 hours after surgery), 2 (44-52 hours after surgery), 4 (90-102 hours), and 7 (158-178 hours after surgery).

Secondary study measures included an evaluation of patient function using the WOMAC questionnaire, knee range of motion (flexion and extension), postoperative ambulation distance, hospital LOS, and opioid consumption. WOMAC score, knee flexion, and knee extension were recorded at baseline, 3 to 4 weeks postoperatively, and 7 to 8 weeks postoperatively. Knee range of motion was measured using a goniometer during office visits. Although liposomal bupivacaine has been shown to last only up to 72 hours [6,7,9,10], we included WOMAC and knee range of motion outcome data up to 8 weeks because early pain control has been shown to affect later functional outcomes [25–28]. Data were collected and recorded by the resident on the arthroplasty service, either in person if the patient was in hospital or by telephone if the patient was discharged. The resident collecting these data was not blinded to the intervention because they likely had been involved in the patient's surgery. Ambulation distance was measured on POD one by a physical therapist during inpatient rehabilitation. Hospital LOS was measured based on the number of nights each patient stayed in the hospital after surgery before being discharged. Opioid consumption was abstracted from the electronic medical record as morphine-equivalent opioid use preoperatively, intraoperatively, on POD zero, on POD one, and the amount prescribed at discharge. Patient medical records were reviewed to determine the number of participants with any opioid prescription refills within 8 weeks of surgery.

Preoperative age, weight, and BMI were compared across groups using 2 sample t-tests. A Pearson's Chi-squared test was used to compare gender across treatment groups. Study outcomes of VAS pain scores, WOMAC score, knee range of motion, and ambulation distance were compared between treatment groups at each recorded time point through 2 sample t-tests, and LOS was categorized (1 day or 2 days) and then compared across treatment groups using Fisher's Exact Test. Mixed effects models were used to further explore the relationship between study outcomes and treatment groups over time for VAS pain scores, WOMAC, knee flexion, and knee extension. For each model, measurement time-point and treatment group were included as fixed effects with random intercepts by patient and random slopes by time-point.

**Table 1**
Demographics and preoperative measurements.

| Demographics | LB-PAI group (N = 27) | ACB group (N = 29) | *P* value[a] |
|---|---|---|---|
| Average age (SD) | 69.5 (7.2) | 66.2 (8.3) | .1 |
| Min, Max | 57, 85 | 54, 84 | |
| Gender % (N) | | | .9 |
| Male | 37.0% (10) | 41.4% (12) | |
| Female | 63.0% (17) | 58.6%% (17) | |
| Average BMI (SD) | 32.4 (4.7) | 34.1 (6.8) | .3 |
| Min, Max | 24.8, 41.3 | 24.3, 47.9 | |

Table 1 shows no significant difference between groups in age, gender, or BMI.
[a] From 2 sample t-tests for age and BMI, and chi-squared test for gender.

With 30 subjects in each treatment group, with a type I error of 0.05, and assuming a pooled standard deviation of 2 points, this study had 80% power to detect a difference in average VAS scores between groups of 1.47 points. A difference in VAS of 3 points is considered a clinically important difference in pain severity; therefore, this study was adequately powered for the primary outcome of interest [29].

## Results

One hundred and fifty-five patients were assessed for eligibility, and 98 of these patients did not meet eligibility criteria or declined to participate (Supplementary Figure 1). Fifty-seven patients consented to the study, including 3 patients who had bilateral TKAs performed in separate procedures (3-4 months apart). Thus, 60 procedures were randomized; LB-PAI was administered in 30 TKA procedures, and ACB was administered in 30 TKA procedures. For analysis, the second procedure for the 3 patients with bilateral TKAs was excluded to ensure independent observations. One additional patient in the LB-PAI group was excluded from analyses because they were retrospectively determined to be opioid dependent at the time of surgery. This led to a total of 29 patients in the LB-PAI group and 27 patients in the ACB group.

There were no significant differences in age, gender, and BMI between the ACB and LB-PAI groups (Table 1). The average age was 66 for the ACB group and 69.5 for the LB-PAI group. More females than males were included in both study groups.

Table 2 shows results of unadjusted analysis comparing study outcomes at each recorded timepoint. Results showed no statistically significant differences in study outcomes across groups at any timepoint. The difference in average VAS scores across treatment groups was small at each timepoint, ranging from 0.03 to 0.9.

When exploring outcomes of VAS pain scores, WOMAC, knee flexion, and knee extension over time through linear mixed effects models, no significant differences were observed between the LB-PAI and the ACB group at any time point. VAS pain scores were found to be significantly higher on POD 2 than on POD 0 (estimate = 1.0-point increase, 95% CI = 0.4, 1.6, $P = .002$) in both study groups (Fig. 1). WOMAC scores were significantly increased from preoperative period to both 3-4 weeks (estimate = 22.2% increase, 95% CI = 16.7, 27.7, $P < .001$) and 7-8 weeks postoperatively (estimate = 31.3% increase, 95% CI = 25.4, 37.2, $P < .001$) (Fig. 2). Knee flexion significantly decreased from preoperative period to 3-4 weeks postoperatively (estimate = −11.9-degree decrease, 95% CI = −15.5, −8.4, $P < .001$) (Fig. 3). Knee extension significantly increased from preoperative period to 3-4 weeks postoperatively (estimate = 2.5-degree increase, 95% CI = 0.8, 4.3, $P < .01$) (Fig. 4). No other significant differences were observed over time for secondary study outcomes.

There was no significant difference between groups in morphine-equivalent opioid use preoperatively, on POD 0, on POD 1, or in the amount prescribed at discharge (Table 3). The percentage of patients requiring a refill within 8 weeks was higher for the ACB group (41% vs 22%), but this was not statistically significant ($P$ value = .2). Although we did not control the amount of opioids prescribed at discharge, our hospital's routine arthroplasty protocol is to prescribe 450-500 milligrams of morphine equivalent opioids in the form of oxycodone, dilaudid, or hydrocodone on discharge.

No patients had serious adverse events in the 8 weeks after surgery. Three patients were readmitted within 30 days of surgery, but all 3 were determined to be unrelated to the study. One patient

**Table 2**
Study outcomes.

| | LB-PAI (N = 27) | ACB (N = 29) | Average difference (95% CI) | *P* value[a] |
|---|---|---|---|---|
| VAS score | | | | |
| Average VAS score at POD 0 (SD) | 2.3 (2.2) | 2.8 (2.2) | 0.5 (-0.7, 1.7) | .4 |
| Average VAS score at POD 1 (SD) | 2.1 (1.6) | 3.1 (2.3) | 0.9 (−0.1, 2.0) | .1 |
| Average VAS score at POD 2 (SD) | 4.1 (1.8) | 4.3 (2.0) | 0.2 (−0.8, 1.3) | .6 |
| Average VAS score at POD 4 (SD) | 3.0 (2.0) | 3.0 (2.4) | 0.04 (−1.0, 1.1) | .9 |
| Average VAS score at POD 7 (SD) | 2.6 (1.8) | 2.6 (2.0) | 0.03 (−1.0, 1.1) | .9 |
| WOMAC score | | | | |
| Average WOMAC score at baseline (SD) | 44.6 (16.8) | 45.0 (17.0) | 0.4 (−8.7, 9.5) | .9 |
| Average WOMAC score at 3-4 weeks postop (SD) | 68.4 (12.2) | 65.9 (16.1) | −2.5 (−10.3, 5.3) | .5 |
| Average WOMAC score at 7-8 weeks postop (SD) | 77.6 (11.2) | 75.1 (18.0) | −2.5 (−11.0, 5.9) | .5 |
| Knee flexion | | | | |
| Average knee flexion at baseline (SD) | 113.4 (14.4) | 114.8 (8.1) | 1.4 (−4.8, 7.6) | .6 |
| Average knee flexion at 3-4 weeks postop (SD) | 102.6 (12.8) | 101.4 (10.5) | −1.2 (−7.4, 5.1) | .7 |
| Average knee flexion at 7-8 weeks postop (SD) | 114.7 (9.1) | 114.0 (8.6) | −0.7 (−5.4, 4.1) | .8 |
| Knee extension | | | | |
| Average knee extension at baseline (SD) | −1.2 (5.6) | 2.0 (7.1) | 3.2 (−0.3, 6.6) | .1 |
| Average knee extension at 3-4 weeks postop (SD) | 2.3 (4.1) | 3.9 (2.7) | 1.6 (−1.7, 4.9) | .3 |
| Average knee extension at 7-8 weeks postop (SD) | 1.9 (4.1) | 1.1 (2.7) | −0.7 (−2.6, 1.1) | .4 |
| Ambulation distance | | | | |
| Average ambulation distance on POD 1 (SD) | 244.1 (154.6) | 214.0 (112.4) | −30.1 (−103.2, 43.0) | .4 |
| Length of stay | | | | |
| % (N) 1 day | 93% (25) | 93% (27) | - | |
| % (N) 2 days | 7% (2) | 7% (2) | | .99 |

Table 2 illustrates no statistically significant differences in measured outcomes between LB-PAI and ACB groups.
[a] From Fisher's Exact test for length of stay and from 2 sample t-tests for all other outcomes.

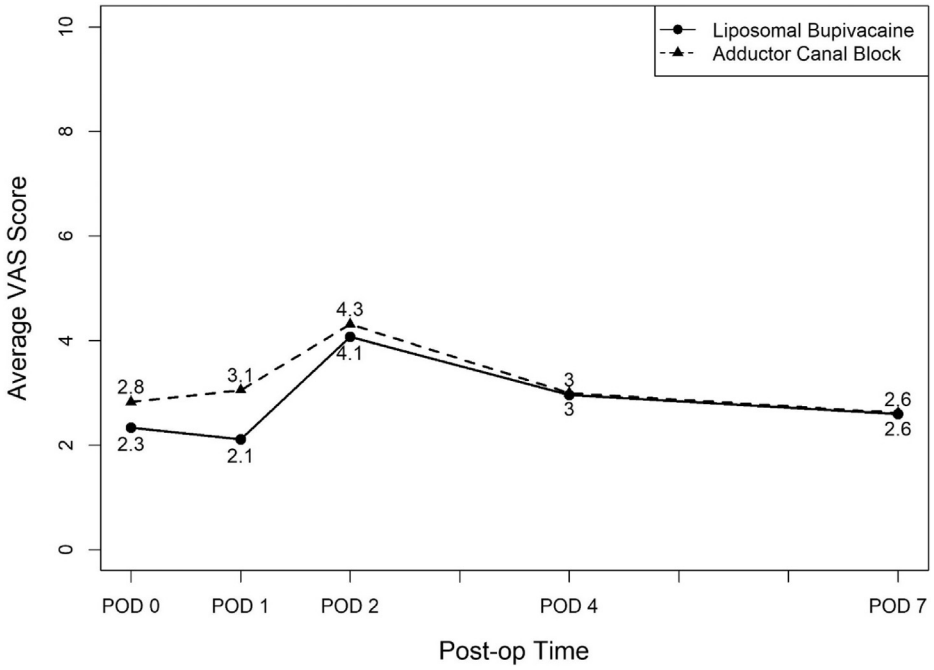


**Figure 1.** Average VAS by study group over time. It illustrates average VAS score for LB-PAI and ACB study groups at any recorded time point.

was a 69-year-old female who was readmitted 2 days after surgery for congestive heart failure exacerbation due to fluid retention. The second patient was a 62-year-old female who was readmitted 4 days after surgery for altered mental status due to polypharmacy. She was taking oxycodone with an old prescription of tramadol, gabapentin, and cyclobenzaprine. The third patient was a 71-year-old female who was readmitted 4 days after surgery for increased somnolence and hypotension due to dehydration. All patients recovered uneventfully after treatment by the hospitalist team and were subsequently discharged.

A cost analysis was performed at the conclusion of the study. A single 266-milligram vial of liposomal bupivacaine (EXPAREL) costs $351 at our institution. A single-shot ACB with bupivacaine performed by the anesthesiologist costs $893, which includes anesthesia procedure charge, medication, and materials.

## Discussion

The goal of this study was to conduct a randomized control trial to directly compare the efficacy of LB-PAI to that of an ACB with bupivacaine HCl in patients with TKA. This study demonstrates that patients treated with LB-PAI perform similarly to patients treated with a single-shot ACB with respect to postoperative pain, WOMAC scores, knee ROM, ambulation distance on POD 1, LOS, and opioid

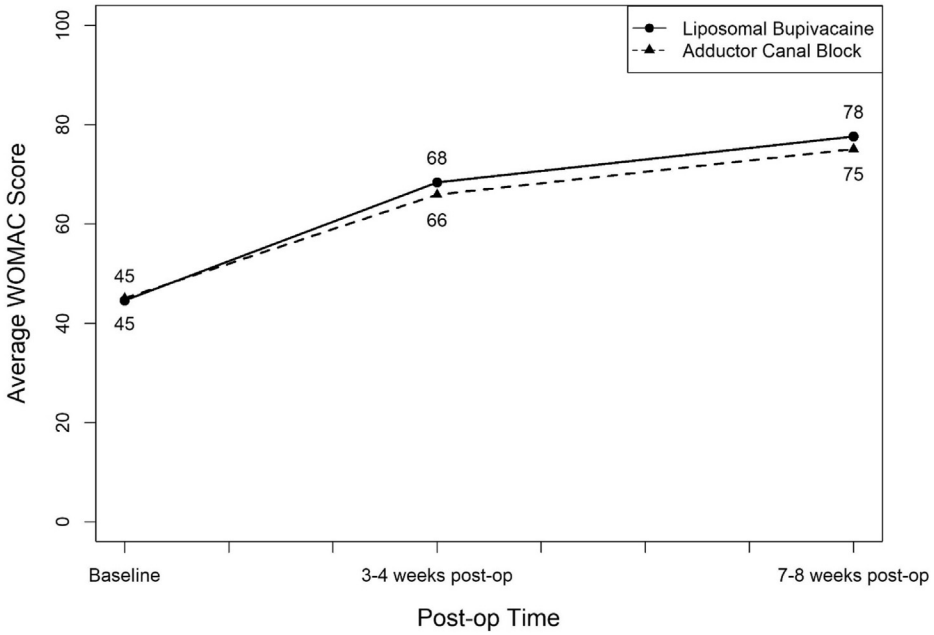


**Figure 2.** Average WOMAC by study group over time. It demonstrates average WOMAC score for LB-PAI and ACB study groups.

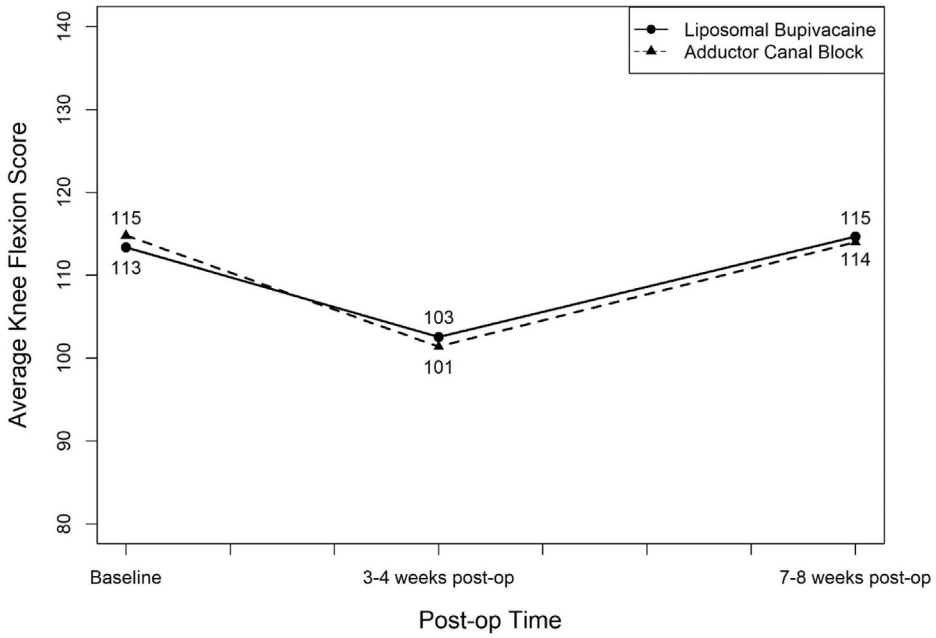


**Figure 3.** Average knee flexion by study group over time. It illustrates average knee flexion for LB-PAI and ACB study groups.

use. This study suggests LB-PAI in TKA has no additional clinical benefit in pain control when compared to ACB with bupivacaine HCl but may confer a cost benefit.

The use of an ACB as part of a multimodal pain management protocol is the current preferred peripheral nerve block at our institution for TKA. However, ACB has multiple disadvantages including the inability to block the posterior and lateral knee innervations, additional time to perform the procedure, risk of block failure, and potential nerve injury [30]. The analgesic effect of ACB is limited to the medial side of the knee by blocking the saphenous and posterior branch of the obturator nerve; however, the lateral and posterior sides of the knee are not targeted [31,32]. LB-PAI is theoretically advantageous in that it allows for administration of local anesthetic agents to all areas of the knee capsule [20]. In addition, patients may avoid the need of undergoing an additional peripheral nerve block procedure and its associated risks. Eliminating the need for a preoperative procedure may reduce operating room turnover time, thus improving operating room efficiency, especially if there is no dedicated regional anesthesia block team available at the institution. Finally, LB-PAI has been shown to be cost-effective when compared with other perioperative analgesic protocols [33]. At our institution, the charge of administering a single-shot ACB including medications, materials, and anesthesiologist procedure fee is $542 more than the charge for

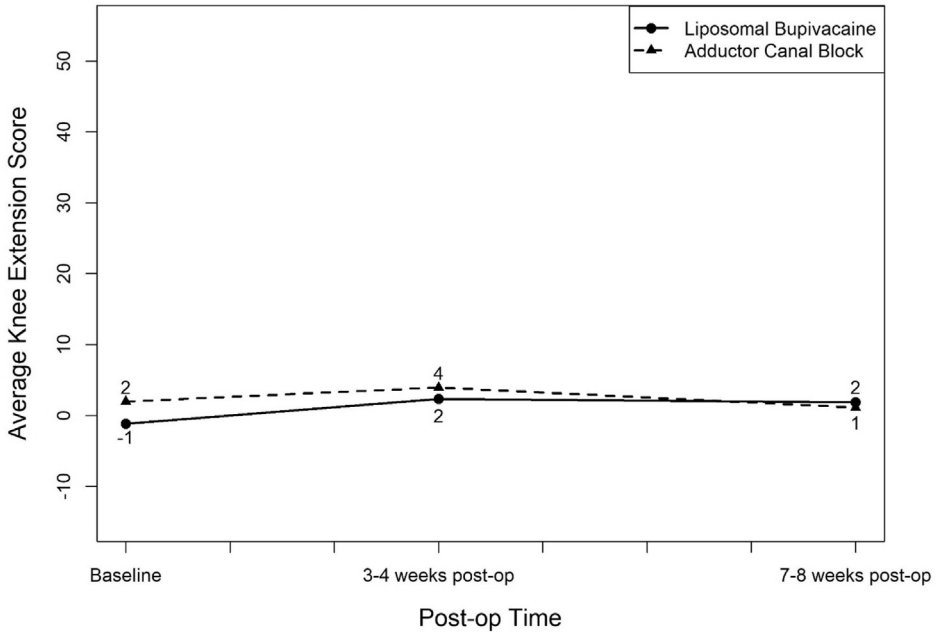


**Figure 4.** Average knee extension by study group over time. It illustrates average knee flexion for LB-PAI and ACB study groups.

**Table 3**
Morphine equivalents (ME) across study groups.

| | LB-PAI (N = 27) | ACB (N = 29) | *P* value[a] |
|---|---|---|---|
| Average inpatient, preop ME (SD) | 5.6 (7.6) | 8.5 (9.6) | .14 |
| Min, Max | 0, 25 | 0, 35 | |
| Median | 0 | 5 | |
| Average inpatient POD 0 ME (SD) | 15.2 (14.3) | 16.5 (17.6) | .9 |
| Min, Max | 0, 45 | 0, 67.5 | |
| Median | 15 | 15 | |
| Average inpatient POD 1 ME (SD) | 21.7 (21.1) | 22.1 (19.2) | .9 |
| Min, Max | 0, 60 | 0, 60 | |
| Median | 15 | 15 | |
| Average total ME prescribed at discharge (SD) | 1019 (437.9) | 1108 (612.1) | .8 |
| Min, Max | 75, 1800 | 0, 3000 | |
| Median | 900 | 900 | |
| % (N) with any refills within 8 weeks | 22% (6) | 41% (12) | .2 |

[a] From Fisher's Exact test for intra-operative ME, chi-squared test for any refills, and from Wilcoxon rank sum tests for all others.

administering a single vial of liposomal bupivacaine. In this era of cost consciousness, it is incumbent on the surgeon to help contain cost when there is an equally efficacious alternative. We recommend surgeons evaluate the cost of the various procedures at their hospital and select the method most financially beneficial to their patients.

LB-PAI in TKA has been compared to different perioperative pain control modalities, including traditional PAI with nonliposomal amide anesthetic agents such as bupivacaine HCl and ropivacaine, and the results have been controversial. Schroer et al. reported that LB-PAI did not improve pain control or reduce narcotic use when compared with bupivacaine HCl [15]. Similarly, Kuang et al. showed in a meta-analysis that LB-PAI offered similar pain control and functional recovery after TKA compared with conventional PAI and did not recommend its use as a long-acting analgesic agent [16]. On the other hand, multiple studies including a meta-analysis by Wang et al. showed superior pain control, less opioid use, and decreased opioid-related adverse events when performing LB-PAI in TKA [10–14]. In a more recent meta-analysis, Liu et al. concluded that liposomal bupivacaine did not improve pain score in TKA but did decrease morphine equivalent consumption and associated nausea and vomiting postoperatively [34]. In a recent randomized controlled trial comparing liposomal bupivacaine to bupivacaine HCl in patients undergoing TKA, Zlotnicki et al. concluded that the 2 preparations were essentially equivalent for pain control [35]. Although the literature surrounding liposomal bupivacaine is controversial, this study was unique in that patients of both treatment arms received a bupivacaine HCl PAI with ketorolac and morphine, allowing for a direct comparison between LB-PAI and ACB.

LB-PAI has been shown to be superior to FNB in TKA with regard to pain control, hospital LOS, narcotic usage, and early rehabilitation potential [17–21,36–38]. Yu et al. [39] showed in a retrospective analysis that patients who received an LB-PAI for TKA had significantly lower fall rates during their hospital stay than those who received FNB. This is an important advantage of PAI, as PAI does not affect quadriceps motor function like FNB does, allowing for safer ambulation and potential for superior rehabilitation. Another advantage is the ability to place anesthetic at all areas of the knee, not just areas covered by the peripheral nerve being blocked [20]. Liposomal bupivacaine may also reduce the risk of sudden onset of pain, due to its slow-release mechanism.

There are limitations to our study. First, the sample size was relatively small. However, the study was still adequately powered to detect a clinically meaningful difference of 3 points or more [29] in the primary outcome of interest, VAS pain scores. To exemplify this, the 95% confidence intervals surrounding differences in average VAS pain scores across treatment groups are in Table 2. These confidence intervals remain within the range of -3 to 3 at each time point. Therefore, at an alpha of 0.05, we can reject the hypothesis that our treatment groups differed by 3 points or more. Given the relatively small sample size, our study may be underpowered to detect clinically significant differences in the secondary outcomes. Larger studies may be warranted to help expand our understanding of the effect of LB-PAI compared with an ACB. In addition, the providers and the patients were not blinded in the study, which may add bias to the outcome scores. Blinding would have caused unnecessary burden to patients by requiring an injection of a placebo ACB in the LB-PAI group and an injection of placebo PAI in the ACB group. Another limitation to note is that our study results are not generalizable to opiate-dependent patients because they were excluded from this study.

## Conclusions

To our knowledge, this is the first randomized control trial directly comparing the efficacy of LB-PAI to that of an ACB. Our findings suggest that compared with an ACB with bupivacaine HCl, LB-PAI offers similar postoperative pain control and functional outcomes at a reduced cost and without additional risks for patients undergoing TKA. In future, larger studies are warranted to help expand our understanding of the effect of LB-PAI compared with an ACB.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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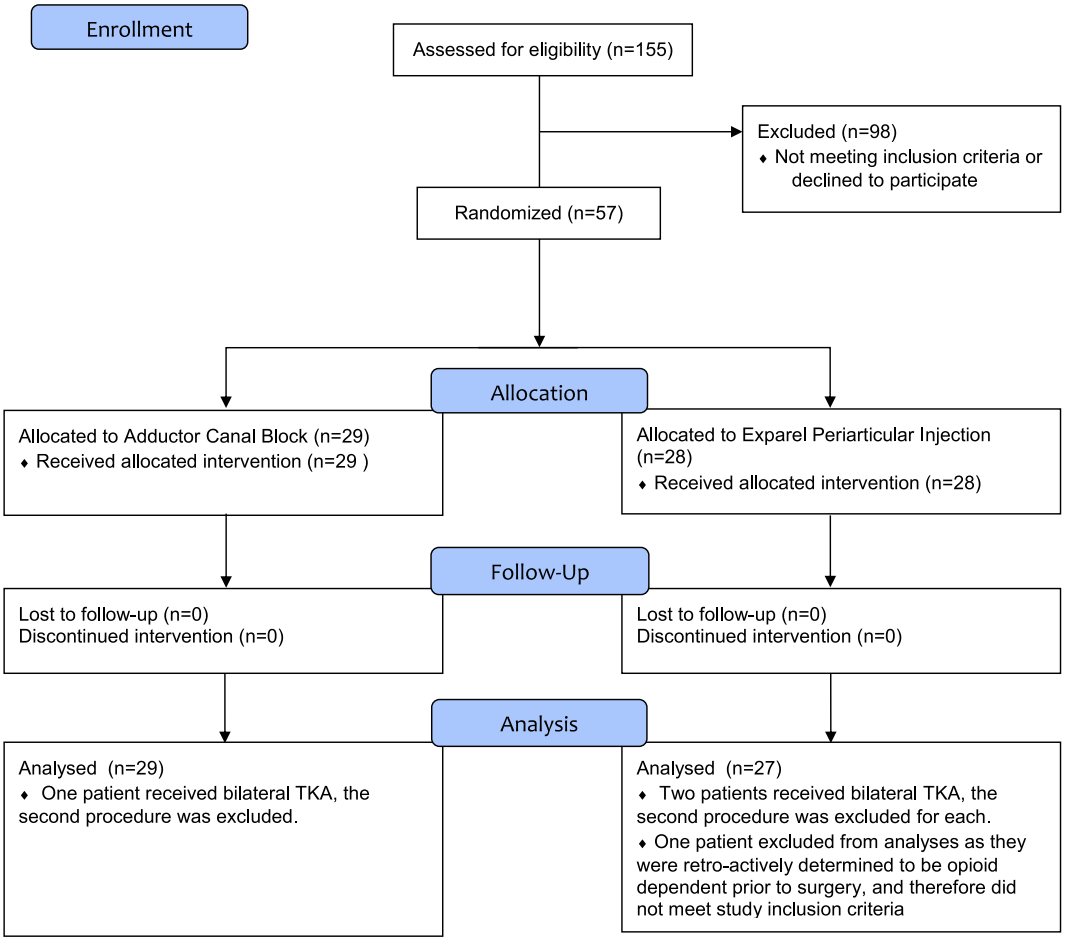


**Supplementary Figure 1.** Study flowchart.