

Liposomal Bupivacaine for Adductor Canal Block Combined with IPACK Block in Total Knee Arthroplasty: A Prospective, Double-Blind, Randomized Controlled Trial

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Purpose: Patients undergoing total knee arthroplasty (TKA) may experience severe postoperative pain despite preoperative nerve blocks. This study aims to investigate the effect of liposomal bupivacaine (LB) for adductor canal block (ACB) combined with infiltration between the popliteal artery and the posterior knee capsule (iPACK) in TKA.

Patients and Methods: This prospective, double-blind, randomized controlled trial was conducted from March 2025 to August 2025 in a Chinese tertiary hospital. 86 patients aged 18–90 years, classified as the American Society of Anesthesiologists (ASA) Physical Status I–III and undergoing TKA, were randomly assigned to either the liposomal bupivacaine group (Group LB) or ropivacaine group (Group R). All patients underwent ACB combined with iPACK block administered with either LB or ropivacaine preoperatively. The primary outcome was visual analog scale (VAS) at multiple time points under three conditions: at rest, during maximum knee flexion, and during ambulation. Secondary outcomes included opioids consumption, knee range of motion (ROM), quadriceps strength, the Timed Up-and-Go (TUG) test within the first 3 days, as well as the American Knee Society (AKS) score and the Quality of Recovery-15 (QoR-15) score assessed at 2 weeks and 1 month.

Results: Demographic and baseline characteristics were comparable between groups ($P > 0.05$). The VAS scores in Group LB were significantly lower than those in Group R at 24h, 48h, and 72h across all assessment conditions ($P < 0.05$). However, these differences did not reach the minimal clinically important difference (MCID). From 48h to 72h, opioids consumption in Group LB was significantly lower than that in Group R ($P < 0.05$), but again not clinically significant. No significant differences were observed between groups in other outcomes ($P > 0.05$).

Conclusion: Liposomal Bupivacaine for adductor canal block combined with IPACK block provided no clinically significant benefit in patients undergoing total knee arthroplasty.

Keywords: liposomal bupivacaine, adductor canal block, iPACK block, total knee arthroplasty

Introduction

The rate of total knee arthroplasty (TKA) has been increasing in recent years due to factors such as population aging, rising obesity rates, and the easing of the COVID-19 pandemic.^{1,2} Postoperative pain is a distressing complication in patients who undergo TKA, affecting nearly 60% of patients.³ Severe pain frequently impedes early functional exercise, delaying recovery.⁴ Consequently, effective pain management is a priority for surgeons and anesthesiologists.

Although opioids effectively treat intense pain, prolonged administration can cause adverse effects and increase revision risk within the first year.⁵ Current guidelines recommend multimodal analgesia for TKA, including paracetamol, non-steroidal anti-inflammatory drug, nerve blocks and local infiltration analgesia.^{3,6} The combination of adductor canal block (ACB) and infiltration between the popliteal artery and the posterior knee capsule (iPACK) has emerged as an effective postoperative analgesia strategy, helping to reduce postoperative pain and promote mobility without increasing side effects.⁷ ACB targets the saphenous nerve to alleviate anteromedial and intra-articular knee pain while sparing motor function.⁸ Similarly, iPACK anesthetizes terminal branches of the genicular nerves and popliteal plexus without blocking the tibial or common peroneal nerves, preserving muscle strength.⁹

Commonly used local anesthetics (eg, bupivacaine, ropivacaine) are limited by their short duration of action.¹⁰ Liposomal bupivacaine (LB), a novel sustained-release formulation, encapsulates aqueous bupivacaine within lipid bilayer vesicles.¹¹ This structure enables controlled drug release for up to 120 hours.¹² It was reported that LB can help alleviate postoperative pain after TKA.¹³ Meanwhile, another study did not find that applying LB for ACB could provide better pain relief.¹⁴ Therefore, there is no consensus on the application of LB in TKA pain management so far and further studies are necessary.

Currently, there are few studies evaluating the effect of LB on combined ACB-iPACK blocks. Therefore, we conducted a prospective, double-blind, randomized controlled trial to compare LB with ropivacaine for combined ACB-iPACK blocks in TKA, with the aim of providing reference for clinical practice. We hypothesized that LB would provide better postoperative analgesia than ropivacaine.

Materials and Methods

Ethics and Patients

Following approval from Shanghai East Hospital Medical Ethics Committee (2025YS-001) and registration with the Chinese Clinical Trial Registry (ChiCTR2500096662), this prospective, double-blind, randomized controlled trial was conducted between March 2025 and August 2025 in a Chinese tertiary hospital, in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. The study adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

The inclusion criteria are as follows: (1) aged 18–90 years, (2) body mass index (BMI) 18–35 kg/m², (3) diagnosed with knee osteoarthritis by a senior orthopedic surgeon and scheduled for primary unilateral TKA, (4) the American Society of Anesthesiologists (ASA) Physical Status I–III. The exclusion criteria are as follows: (1) contraindications to peripheral nerve blocks, (2) a varus-valgus deformity of >20°, knee flexion deformity >30°, (3) poor-controlled hypertension, diabetes, cardiac diseases and malignant tumor, (4) infection at the proposed block puncture sites, (5) chronic opioids use, (6) allergy to LB or ropivacaine, (7) pregnant or breastfeeding, (8) suffering from other painful diseases, (9) participation in other clinical trials.

Randomization and Blinding

Randomization was performed using a R-software-generated sequence (<http://www.R-project.org>; Version 4.2.1) with a 1:1 allocation ratio between the liposomal bupivacaine group (Group LB) and the ropivacaine group (Group R). An independent nurse, not otherwise involved in the study, generated and managed the allocation sequence to minimize assignment bias. Allocation concealment was ensured using sequentially numbered, sealed, opaque envelopes prepared in advance. These envelopes were securely stored and inaccessible to personnel involved in participant recruitment, data collection, or clinical care until the point of allocation. Upon arrival in the operating room, the attending anesthesiologist opened the envelope to reveal group assignment.

For double-blinding, A board-certified regional anesthesiologist, independent of all other study phases, performed the nerve blocks. A separate nurse prepared and administered the assigned local anesthetic solution, preventing the performing anesthesiologist from identifying the drug used. Two independent qualified physicians, serving as outcome assessors blinded to group allocation, jointly evaluated all study endpoints. The statistician performing the final analysis

remained blinded to group assignments. Patients, surgeons, intraoperative anesthesia providers, postoperative care providers, and the statistician were blinded throughout the trial duration.

Nerve Blocks Procedure

Ten minutes before general anesthesia, nerve blocks were completed under ultrasound guidance. All patients received oxygen inhalation, venous access establishment, and standard monitoring prior to nerve blocks. The local anesthetics prepared by the study nurse were as follows: patients in Group LB received 266 mg of liposomal bupivacaine (Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, Jiangsu, China) diluted with saline to 40 mL, while patients in Group R received 100 mg of ropivacaine (Jiangsu Hengrui Pharmaceuticals Co., Ltd., Lianyungang, Jiangsu, China) diluted with saline to 40 mL.

For performing the iPACK block, patients were placed in a prone position. The tibial nerve, generally located near the popliteal crease and superficial to the popliteal vessels, was identified using a high-frequency linear array transducer positioned perpendicularly. Then, the transducer was advanced distally towards the popliteal crease gradually until the femoral condyles were clearly delineated on ultrasound imaging. The needle was inserted laterally and advanced medially, reaching the intercondylar fossa situated between the popliteal artery and the femoral condyles. With the needle tip anterior to the medial femoral condyles, 20 mL of anesthetics was injected and slowly withdrawn until the end of the lateral femoral condyles (Figure 1A).

Subsequently, patients were repositioned into the supine position to conduct ACB. Under ultrasound guidance, the adductor canal was visualized at the mid-thigh. The needle was then inserted into the fascia of the sartorius muscle. Absence of blood on aspiration permitted injection of a small volume of saline to ensure proper needle tip location. Then 20 mL of anesthetics was administered into the adductor canal (Figure 1B).

General Anesthesia Procedure

All patients received standard monitoring and optional invasive blood pressure monitoring. To induce anaesthesia, we administered propofol 1.5 mg/kg, sufentanil 0.3 µg/kg, rocuronium 0.6 mg/kg intravenously and subsequently inserted a laryngeal mask to achieve mechanical ventilation. During anesthesia, propofol infusion was manually adjusted to maintain a bispectral index of 45–55. Remifentanyl 0.15–0.2 µg/kg/min was infused for intraoperative analgesia. After the surgery, the removal of the laryngeal mask was performed in the operating room and each patient was transferred subsequently to a post-anesthesia care unit (PACU).

Surgical Techniques

Two experienced orthopedic surgeons executed all TKA surgeries utilizing the standard medial parapatellar approach. Each surgery was done with a tourniquet inflated to 250 mmHg and the infrapatellar fat pad was routinely excised.

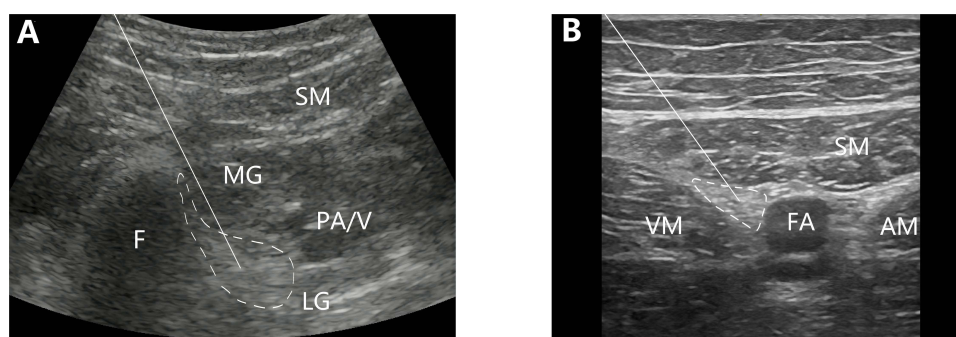


Figure 1 Ultrasound images of infiltration between the popliteal artery and the posterior knee capsule (A) and adductor canal block (B). The solid line represents the needle, and the area within the dashed line represents the injection zone.

Abbreviations: SM, sartorius muscle; MG, medial gastrocnemius; F, femur; PA/V, popliteal artery and vein; LG, lateral gastrocnemius; VM, vastus medialis; FA, femoral artery; AM, adductor magnus.

Cemented, fixed bearings, and posterior-stabilized TKA implants (DePuy Synthes, Raynham, MA, USA) were implanted.

Postoperative Management

In PACU, a cold pack was applied to alleviate pain at the surgical site until roughly 8 hours post-surgery. Intravenous administration of dexamethasone 5 mg and ondansetron 4 mg was utilized for prophylaxis against postoperative nausea and vomiting. If patients experienced severe pain, they were administered flurbiprofen 50 mg intravenously.

Upon transfer to the ward, all patients were prescribed a regimen of drug-based analgesia, which included intravenous flurbiprofen (50 mg per dose, twice daily) and oral pregabalin (75 mg per dose, once daily). For severe postoperative pain, rescue analgesia was provided in the form of a 10 mg oxycodone hydrochloride tablet, not to exceed four times per day.

Enoxaparin was routinely administered subcutaneously at a dose of 2000 IU, 6 hours postoperatively, with subsequent doses of 4000 IU given at 24-hour intervals until discharge. Following discharge, patients were prescribed rivaroxaban, 10 mg taken orally, for a duration of 10 days.

Outcome Measurement

The primary outcome was pain severity, assessed using the visual analog scale (VAS) at multiple postoperative time points across different conditions, including at rest, during maximum knee flexion, and during ambulation.¹⁵ The VAS evaluation time points were within PACU, at 6h, 12h, 24h, 48h, 72h, 2 weeks and 1 month postoperatively.

Secondary outcomes are as follow: (1) daily and total opioids consumption, converted to the oral morphine equivalents, (2) knee range of motion (ROM) at 24h, 48h, and 72h postoperatively, (3) quadriceps strength at 24h, 48h, and 72h postoperatively, (4) timed up-and-go (TUG) test at 24h, 48h, and 72h postoperatively, (5) the American Knee Society (AKS) score at 2 weeks and 1 month postoperatively, (6) the Quality of Recovery-15 (QoR-15) score at 2 weeks and 1 month postoperatively. Quadriceps strength was evaluated utilizing manual muscle testing and graded on a scale from 0 to 5.¹⁵ The TUG test, a measure of ambulatory function, requires the participant to perform the following sequence: rising from an armchair, walking a three-meter distance, turning, walking back, and sitting down again.¹⁶ The AKS score comprises both clinical and functional components for assessing knee function, with a score range of 0 to 100 points respectively.¹⁷ The QoR-15 score consists of 15 questions, which encompass physical comfort, emotional state, physical independence, psychological support, and pain assessment, with a score range of 0 to 150 points.¹⁸

Additionally, we recorded intraoperative data, which included surgery time, tourniquet time, remifentanyl dosage, estimated infusion volume, estimated blood loss, incidence of hypotension, extubation time (the time from the end of surgery to extubation), and time in PACU. Postoperative adverse events, such as central nervous system and cardiovascular adverse events, as well as puncture site hematoma or infection were also documented.

Statistical Analysis

The sample size was calculated in relation to the VAS score. Our preliminary study included 20 patients who underwent combined ACB-iPACK blocks administered with ropivacaine prior to TKA. The mean VAS score on flexion was 4.5 ± 1.2 at 24h postoperatively. A between-group difference in VAS scores exceeding 1.0 was considered clinically significant, as it has been associated with increased morphine consumption.¹⁹ Using PASS 13.0 software (NCSS, Kaysville, UT, USA), and based on an α of 0.05 and a power of 90%, this trial required 36 patients per group to test this difference. To account for potential dropouts of 15%, the sample size was at least 42 per group.

We performed modified intention-to-treat analyses including all patients who were allocated with primary outcome data available. Missing data were not imputed. The normal distribution of the variables was examined using the Kolmogorov–Smirnov test. Continuous data were presented as mean $\pm$ standard deviation and compared using the unpaired, 2-tailed *t* test if distributed normally. Categorical variables were reported as number (%) and compared using χ^2 or Fisher exact test, as appropriate. The interventional effect of the two groups was analyzed further using odds ratio (OR) or mean difference with 95% confidence intervals (CI). Two-sided $P < 0.05$ was considered to be statistically significant. We completed statistical analyses based on SPSS 26.0 (SPSS, Chicago, IL, USA).

Results

A total of one hundred and fourteen patients from a tertiary hospital in China were enrolled in this study (Figure 2). Nine patients refused to participate research. The surgeries for five patients were cancelled. Four patients were suffering chronic pain. Four patients had uncontrolled hypertension. Two patients had severe cardiac diseases. Two patients from each group were excluded due to the unavailability of their primary outcome measures. Eventually, eighty-six patients were divided into two groups: Group LB (n = 43) and Group R (n = 43). All randomized patients strictly received the allocated nerve block interventions as assigned, with no protocol deviations. The demographic data in terms of age, gender, height, body mass index (BMI), ASA classification, smoking status, occupation status, operation side, and comorbidities were similar in both groups. Besides, there were no significant differences between the two groups for preoperative knee ROM, quadriceps strength, VAS scores, TUG test, AKS scores and QoR-15 score (Table 1).

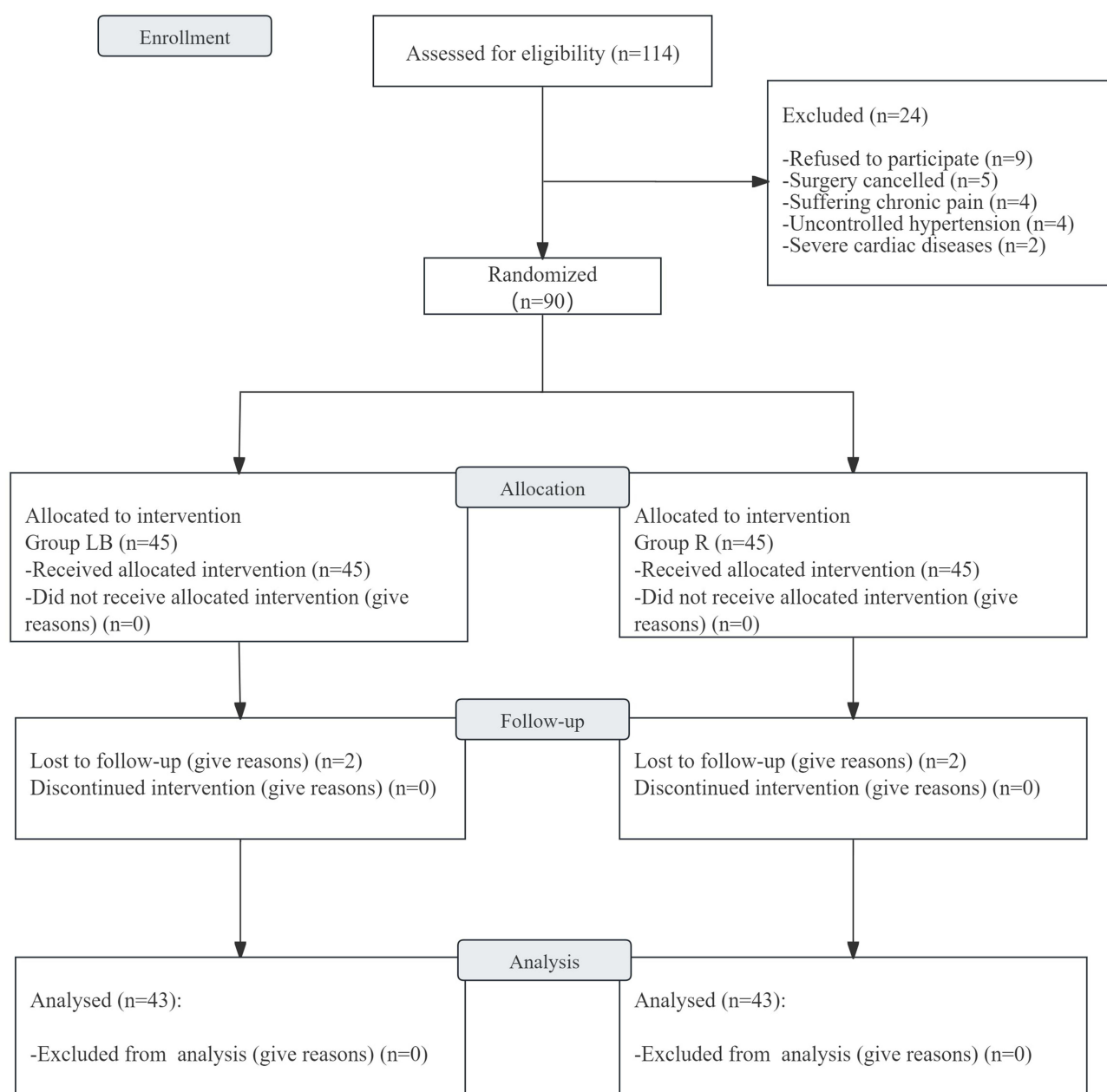


Figure 2 Study Flow Diagram.

Abbreviations: R, ropivacaine; LB, liposomal bupivacaine.

Table 1 Demographic and Baseline Characteristics of Patients

Characteristics	Group R (n = 43)	Group LB (n = 43)	Mean Difference or Odds Ratio (95% CI)	P value
Demographic characteristics				
Age (y)	68.0 ± 8.8	67.1 ± 8.2	0.9 (−2.7–4.6)	0.614
Gender (Male/Female)	9/34	7/36	1.36 (0.45–4.09)	0.579
Height (m)	1.58 ± 0.08	1.59 ± 0.08	−0.02 (−0.05–0.02)	0.392
BMI (kg/m ²)	24.1 ± 2.6	24.5 ± 3.1	−0.4 (−1.6–0.9)	0.571
ASA classification (I/II/III)	2/29/12	4/26/13	–	0.915
Current smoker	8 (19%)	11 (26%)	0.66 (0.24–1.81)	0.436
Retiree	35 (81%)	37 (86%)	0.71 (0.24–2.10)	0.559
Operation side (Left/Right)	25/18	20/23	1.60 (0.70–3.68)	0.280
Comorbidities				
Hypertension	22 (51%)	24 (56%)	0.83 (0.36–1.92)	0.666
Diabetes	13 (30%)	17 (40%)	0.66 (0.27–1.60)	0.366
Cardiac diseases	5 (12%)	3 (7%)	1.75 (0.40–7.73)	0.972
Physical examination				
Knee ROM (°)	97.0 ± 8.5	96.4 ± 9.8	0.6 (−0.1–1.3)	0.085
Quadriceps strength	4.7 ± 0.6	4.7 ± 0.5	0 (−0.1–0)	0.093
VAS scores				
Rest	2.61 ± 0.73	2.64 ± 0.61	−0.03 (−0.08–0.02)	0.206
Flexion	5.57 ± 0.98	5.52 ± 1.43	0.05 (−0.05–0.15)	0.305
Ambulation	4.97 ± 1.13	4.94 ± 1.21	0.03 (−0.06–0.11)	0.548
TUG test (s)	27.2 ± 7.3	27.7 ± 9.3	−0.5 (−1.2–0.1)	0.125
AKS scores				
Clinical score	50.1 ± 8.4	50.6 ± 9.3	−0.5 (−1.2–0.2)	0.139
Functional score	48.4 ± 8.9	47.8 ± 9.2	0.6 (−0.1–1.3)	0.082
QoR-15 score	115.9 ± 13.5	115.0 ± 12.9	0.9 (0–1.9)	0.053

Notes: Data presented as mean ± standard deviation were compared using the unpaired, 2-tailed *t* test. Data presented as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test.

Abbreviations: R, ropivacaine; LB, liposomal bupivacaine; CI, confidence intervals; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists; ROM, range of motion; VAS, visual analog scales; TUG, timed up-and-go; AKS, American Knee Society; QoR-15, Quality of Recovery-15.

Intraoperative Outcomes

Surgery time, tourniquet time, remifentanyl dosage, estimated infusion volume, estimated blood loss, incidence of hypotension, extubation time, and time in PACU were not different between the two groups (Table 2).

Table 2 Intraoperative Data of Patients

	Group R (n = 43)	Group LB (n = 43)	Mean Difference or Odds Ratio (95% CI)	P value
Surgery time (min)	88.2 ± 9.7	87.6 ± 8.0	0.6 (0–1.2)	0.066
Tourniquet time (min)	60.2 ± 6.8	59.9 ± 5.4	0.3 (−0.1–0.7)	0.226
Remifentanyl dosage (μg/kg/h)	8.3 ± 1.1	8.4 ± 1.2	−0.1 (−0.2–0)	0.075
Estimated infusion volume (mL)	1201 ± 331	1210 ± 239	−9 (−29–10)	0.345
Estimated blood loss (mL)	286 ± 33	287 ± 36	−1 (−4–1)	0.358
Incidence of hypotension	11 (26%)	13 (30%)	0.79 (0.30–2.07)	0.631
Extubation time (min)	9.8 ± 2.0	9.9 ± 1.8	−0.1 (−0.2–0)	0.111
Time in PACU (min)	35.1 ± 3.1	35.0 ± 3.1	0.2 (−0.1–0.4)	0.162

Notes: Data presented as mean ± standard deviation were compared using the unpaired, 2-tailed *t* test. Data presented as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test.

Abbreviations: R, ropivacaine; LB, liposomal bupivacaine; CI, confidence intervals; PACU, post-anesthesia care unit.

Postoperative Pain Assessments

At rest, patients in Group LB showed significantly lower VAS score than Group R at 24h (3.28 ± 0.94 vs 3.70 ± 1.37 , $P < 0.001$), 48h (3.14 ± 1.21 vs 3.26 ± 1.07 , $P = 0.009$), and 72h (2.96 ± 1.12 vs 3.38 ± 1.15 , $P < 0.001$) postoperatively.

During maximum knee flexion, patients in Group LB showed significantly lower VAS score than Group R at 24h (4.97 ± 1.07 vs 5.07 ± 0.82 , $P = 0.008$), 48h (4.60 ± 1.32 vs 4.85 ± 1.40 , $P < 0.001$), and 72h (4.05 ± 1.06 vs 4.16 ± 1.24 , $P = 0.011$) postoperatively.

During ambulation, Group LB showed significantly lower VAS score than Group R at 24h (4.51 ± 1.02 vs 4.82 ± 0.83 , $P < 0.001$), 48h (4.32 ± 0.66 vs 4.58 ± 0.67 , $P < 0.001$), and 72h (3.84 ± 0.78 vs 4.14 ± 0.71 , $P < 0.001$) postoperatively.

However, all the difference between the two groups did not reach the minimal clinically important difference (MCID) of 1.0 (Table 3).¹⁹

Other Postoperative Assessments

Group LB had fewer opioids consumption from 48h to 72h postoperatively than Group R (29.3 ± 16.5 vs 38.6 ± 22.4 , $P = 0.031$). Moreover, no significant difference was observed in opioids consumption between the two groups within 24h or from 48h to 72h ($P > 0.05$) (Table 4).

No significant differences were found between the two groups in other postoperative outcomes, including knee ROM, quadriceps strength, and TUG test at 24h, 48h, and 72h, as well as AKS scores and QoR-15 scores at 2 weeks and 1 month postoperatively ($P > 0.05$) (Table 4).

Table 3 Comparison of Postoperative Visual Analog Scales

	Group R (n = 43)	Group LB (n = 43)	Mean Difference (95% CI)	P value
At rest				
Within PACU	2.35 ± 0.79	2.30 ± 0.79	0.05 (−0.01–0.10)	0.114
6h	2.58 ± 0.65	2.56 ± 0.49	0.03 (−0.01–0.07)	0.188
12h	2.90 ± 0.67	2.94 ± 0.83	−0.03 (−0.09–0.03)	0.266
24h	3.70 ± 1.37	3.28 ± 0.94	0.42 (0.34–0.50)	< 0.001 ^a
48h	3.26 ± 1.07	3.14 ± 1.21	0.12 (0.03–0.20)	0.009 ^a
72h	3.38 ± 1.15	2.96 ± 1.12	0.42 (0.34–0.50)	< 0.001 ^a
2 weeks	1.48 ± 0.33	1.46 ± 0.36	0.02 (0–0.04)	0.169
1 month	0.76 ± 0.33	0.75 ± 0.37	0.01 (−0.02–0.04)	0.450
During maximum knee flexion				
Within PACU	4.34 ± 0.95	4.31 ± 1.20	0.02 (−0.06–0.11)	0.566
6h	4.57 ± 1.80	4.64 ± 1.31	−0.07 (−0.18–0.03)	0.173
12h	3.98 ± 0.65	3.95 ± 0.67	0.02 (−0.06–0.11)	0.179
24h	5.07 ± 0.82	4.97 ± 1.07	0.10 (0.03–0.18)	0.008 ^a
48h	4.85 ± 1.40	4.60 ± 1.32	0.25 (0.15–0.35)	< 0.001 ^a
72h	4.16 ± 1.24	4.05 ± 1.06	0.11 (0.02–0.19)	0.011 ^a
2 weeks	2.30 ± 0.59	2.33 ± 0.63	−0.03 (−0.08–0.01)	0.158
1 month	1.52 ± 0.46	1.51 ± 0.47	0.01 (−0.03–0.04)	0.679
During ambulation				
24h	4.82 ± 0.83	4.51 ± 1.02	0.31 (0.16–0.39)	< 0.001 ^a
48h	4.58 ± 0.67	4.32 ± 0.66	0.26 (0.19–0.34)	< 0.001 ^a
72h	4.14 ± 0.71	3.84 ± 0.78	0.30 (0.14–0.41)	< 0.001 ^a
2 weeks	1.96 ± 0.27	1.95 ± 0.34	0.01 (−0.02–0.03)	0.115
1 month	1.01 ± 0.27	0.99 ± 0.32	0.02 (0–0.05)	0.134

Notes: Data presented as mean $\pm$ standard deviation were compared using the unpaired, 2-tailed *t* test. ^athe difference did not reach the minimal clinically important difference of 1.0.

Abbreviations: R, ropivacaine; LB, liposomal bupivacaine; CI, confidence intervals; PACU, post-anesthesia care unit.

Table 4 Comparison of Opioids Consumption and Functional Outcomes Postoperatively

	Group R (n = 43)	Group LB (n = 43)	Mean Difference or Odds Ratio (95% CI)	P value
Opioids consumption (mg)				
Within 24h	25.6 ± 19.7	29.8 ± 22.4	-4.2 (-13.2-4.9)	0.360
24-48h	39.5 ± 24.1	32.6 ± 18.0	7.0 (-2.1-16.1)	0.132
48-72h	38.6 ± 22.4	29.3 ± 16.5	9.3 (0.9-17.8)	0.031 ^a
Total	103.7 ± 41.9	91.6 ± 31.5	12.1 (-3.8-28.0)	0.134
Knee ROM (°)				
24h	87.1 ± 8.1	87.4 ± 8.2	-0.3 (-3.8-3.2)	0.854
48h	100.9 ± 11.3	102.8 ± 10.4	-1.9 (-6.6-2.7)	0.412
72h	108.9 ± 13.9	110.4 ± 10.8	-2.6 (-7.9-2.8)	0.342
Quadriceps strength				
24h	3.4 ± 0.8	3.3 ± 0.7	0.1 (-0.3-0.4)	0.694
48h	4.1 ± 0.9	3.8 ± 0.8	0.3 (-0.1-0.7)	0.102
72h	4.2 ± 0.9	4.0 ± 0.8	0.2 (-0.1-0.6)	0.249
TUG test (s)				
Unable to do test at 24h postoperatively	7 (16.3%)	9 (20.9%)	0.73 (0.25-2.18)	0.579
24h	109.6 ± 9.4	111.5 ± 9.7	-1.9 (-6.4-2.6)	0.405
Unable to do test at 48h postoperatively	2 (4.7%)	1 (2.3%)	2.05 (0.18-23.43)	1.000
48h	87.2 ± 8.1	85.6 ± 8.2	1.6 (-1.9-5.2)	0.365
72h	74.7 ± 5.5	76.0 ± 7.0	-1.2 (-3.9-1.5)	0.377
AKS scores at 2 weeks postoperatively				
Clinical score	66.0 ± 7.1	63.1 ± 6.5	2.8 (-0.1-5.8)	0.057
Functional score	66.0 ± 8.5	65.3 ± 8.2	0.8 (-2.8-4.3)	0.671
AKS scores at 1 month postoperatively				
Clinical score	75.0 ± 9.9	73.9 ± 9.7	1.1 (-3.1-5.3)	0.614
Functional score	73.7 ± 8.4	74.8 ± 7.1	-1.1 (-4.4-2.3)	0.526
QoR-15 scores				
2 weeks	121.3 ± 13.6	122.2 ± 10.9	-0.8 (-6.1-4.5)	0.754
1 month	128.5 ± 10.6	129.2 ± 9.5	-0.7 (-5.0-3.6)	0.749

Notes: Data presented as mean ± standard deviation were compared using the unpaired, 2-tailed *t* test. Data presented as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test. ^athe difference did not reach the minimal clinically important difference of 10 mg.

Abbreviations: R, ropivacaine; LB, liposomal bupivacaine; CI, confidence intervals; ROM, range of motion; TUG, timed up-and-go; AKS, American Knee Society; QoR-15, Quality of Recovery-15.

Adverse Events

The adverse events observed up to 2 weeks postoperatively included postoperative nausea and vomiting in two patients per group, postoperative respiratory depression in an 84-year-old female patient in Group R, and mild postoperative delirium in a 73-year-old male patient in Group LB. No other adverse events were observed. However, these adverse events are considered common complications attributable to the background of general anesthesia and surgery.

Discussion

This prospective, randomized, double-blind controlled trial evaluated the efficacy of LB compared to ropivacaine for combined ACB-iPACK blocks in patients undergoing TKA. Our primary findings indicate that while LB provided a statistically significant reduction in VAS scores at 24h, 48h, and 72h postoperatively, these reductions did not meet the threshold for the MCID. Although LB significantly reduced opioids consumption from 48h to 72h postoperatively compared with ropivacaine, the difference between groups did not reach the MCID (10mg) as well.²⁰ Furthermore, no significant differences were observed between groups in other outcomes, including knee ROM, quadriceps strength, TUG test, AKS scores and QoR-15 scores.

LB, with its extended-release formulation, was developed to prolong the duration of single-injection peripheral nerve blocks, thereby potentially bridging the gap to sustained postoperative pain control.²¹ In this study, the concentrations of LB (0.665%) and ropivacaine (0.25%) reflect common clinical practice doses and are similar to those used in previous research.^{22,23} Malige et al reported that using LB for ACB safely led to decreased pain levels, shorter hospital stays, reduced inpatient opioid usage, and improved motor function.¹³ In contrast to previous studies, this study represents the first instance of LB being used in combination with ACB and iPACK.^{7,13} The iPACK block targets the terminal sensory branches innervating the posterior capsule without causing motor weakness.²⁴ The synergistic use of both blocks, as employed in our protocol, is theorized to provide comprehensive peri-articular analgesia.

However, the statistically significant yet clinically insignificant findings pose a crucial interpretive challenge. The failure to achieve the MCID threshold suggests that the effect size, though detectable under trial conditions, is unlikely to be perceived as meaningful by patients or to alter clinical pathways. This phenomenon may be attributable to the high efficacy of the background multimodal analgesic regimen, which included both pharmacological analgesia and dual-target nerve blocks. This regimen likely established a high level of pain control and functional readiness, thereby diminishing the incremental benefit of any single component, a context in which several studies of LB have struggled to demonstrate clear superiority.^{25,26} In addition, it remains unclear whether surgical drainage affects the concentration of LB within the blockade area. Future studies are warranted to investigate the pharmacokinetic profile of LB when used in both ACB and iPACK blocks. Our results align with several former studies. Hungerford et al reported that there was no significant difference between LB and ropivacaine in ACB, questioning the value of LB in the postoperative analgesia after TKA.¹⁴ Chen et al reported that LB had no advantage in reducing postoperative pain, despite reducing hospitalization time.²⁷

The two groups showed similar outcomes in functional recovery, constituting a compelling evidence of this study. In contemporary TKA, the paramount goal is not merely analgesic efficacy but the rapid restoration of function, especially for elderly patients.²⁸ Preserved quadriceps strength and the achievement of mobilization milestones are directly correlated with long-term patient satisfaction and are the key metrics of a successful recovery protocol.²⁹

Regarding adverse events, the study observed isolated cases of postoperative nausea and vomiting, postoperative respiratory depression, and emergence delirium. However, these events are considered common occurrences attributable to general anesthesia and surgery. Two patients who experienced nausea and vomiting on postoperative day 1 had their symptoms resolved with antiemetic medication. The patient with respiratory depression received pressurized oxygenation in PACU, after which the condition improved and the patient was transferred back to the ward. The patient with delirium was treated with dexmedetomidine in the PACU; the symptoms subsided after two hours, and the patient was subsequently discharged to the ward. Besides, We did not observe systemic toxicity reactions to the local anesthetic. Conventional bupivacaine formulations carry a significant risk of cardiotoxicity, necessitating strict precautions against intravascular injection. Animal studies have demonstrated a favorable safety profile for liposomal bupivacaine.³⁰ Pharmacokinetic studies indicate that, compared to conventional formulations, the liposomal encapsulation reduces the peak plasma concentration of the drug, which likely contributes to the decreased incidence of systemic toxicity reactions.³¹

Beyond efficacy, the economic implications are inescapable. LB represents a substantial cost premium over ropivacaine. In this study, the drug cost for the LB intervention was approximately 13 times greater than ropivacaine. It constitutes a low-value intervention that increases healthcare expenditure without a commensurate return in patient outcomes.

This study has several limitations. Firstly, nerve blocks were performed by three qualified anesthesiologists, and potential variations in their individual techniques may have influenced the effectiveness. Secondly, the study did not collect perioperative blood or urine samples to investigate the microscopic mechanisms of LB. Furthermore, the study did not perform multivariate analyses to identify other factors potentially influencing outcomes.

Conclusion

In conclusion, in patients undergoing TKA who received preoperative combined ACB-iPACK blocks, liposomal bupivacaine provides a pharmacologically extended but clinically irrelevant analgesic effect. It confers no advantage in functional recovery and patient-reported outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Qisong Yuan, Zhaoming Guan and Longqiu Yang were responsible for conceived, designed this study. Yi Zhang and Xinge Lu were responsible for data collection. Wenbin He, Xiaomin Wang, Longqiu Yang, Wang Shen and Feng Liu were responsible for study execution. Wang Shen and Jinyuan Zhang were responsible for manuscript writing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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