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The efficacy of liposomal bupivacaine in parasacral ischial plane block for pain management after total knee arthroplasty: a randomized controlled trial

Xuan Pan[1], Peng Ye[1,2], Ting Zheng[1], Cansheng Gong[1], Chunying Zheng[1,2*] and Xiaochun Zheng[1,2*]

Abstract

Background Utilizing liposomal bupivacaine (LB) for postoperative analgesia post-total knee arthroplasty (TKA) is prevalent. However, its effectiveness in pain control, specifically in the parasacral ischial plane block (PIPB) post-TKA, remains unknown.

Methods This single-center, double-blinded, randomized controlled trial recruited patients scheduled for unilateral TKA. Forty-five patients were randomly assigned in a 1:1 ratio to receive 133 mg (Group A) or 266 mg (Group B) LB using the block randomization method. The PIPB effectiveness was assessed by evaluating changes in sensory and motor functions. The primary outcome was the cumulative area under the curve (AUC) of the Numerical Rating Scale (NRS) at rest within 72 h postoperatively. All patients were included in the analyses of analgesic efficacy, rehabilitation quality, and adverse events.

Results Between January 30, 2024, and May 1, 2024, 45 patients were enrolled and randomly assigned to Group A (n = 22) and Group B (n = 23). A significant between-group difference was observed in the NRS-$AUC_{0\text{-}72\,h}$ at rest postoperatively (132.3 ± 19.7 vs. 97.3 ± 19.1, $p = 0.001$), but none was observed in NRS-$AUC_{0\text{-}72\,h}$ during activity ($p = 0.642$). Kaplan–Meier survival analysis revealed significant between-group differences in the median onset times of sensory [60 vs. 35(min), $p < 0.0001$] and motor blocks [85 vs. 50(min), $p < 0.0001$]. The onset time of sensory block was notably shorter than that of motor block in both groups. No significant variance was observed in the median regression time for the sensory block. A significant between-group difference in the rescue analgesic dosage was observed on the first postoperative day [43.1 vs. 27.2(mg), $p = 0.009$], with no significant differences in the subsequent two days or the total amount. No significant between-group differences were found in adverse events or rehabilitation quality.

Conclusion LB used in the PIPB was effective for analgesia at rest post-TKA, with 266 mg demonstrating superiority.

*Trial Registration*The randomized controlled trial was registered in the Chinese Clinical Trial Registry (https://www.chictr.org.cn/, No: ChiCTR2400079606)

Keywords Liposomal bupivacaine, Postoperative analgesia, Total knee arthroplasty, Parasacral ischial plane block

[†]Xuan Pan, Peng Ye, and Ting Zheng have contributed equally to this work.

[†]Chunying Zheng and Xiaochun Zheng are co-corresponding authors.

*Correspondence:
Chunying Zheng
373747832@qq.com
Xiaochun Zheng
fjslmzk7841@163.com
Full list of author information is available at the end of the article

Introduction

Total knee arthroplasty (TKA) is a primary treatment option for patients with end-stage knee osteoarthritis, [1, 2] with millions of procedures performed annually. The primary aim of TKA is to restore the patient's neutral mechanical axis, thereby enhancing the functional rehabilitation of the knee [3]. However, TKA often leads to significant postoperative pain due to its impact on the knee capsule and periosteum [4]. Currently, 60% of patients experience severe postoperative pain, which may persist for 3–4 days or longer post-surgery [5, 6].

Clinical guidelines recommend a multimodal approach to enhance analgesic quality and improve rehabilitation outcomes post-TKA [7–9]. Peripheral nerve blocks (PNBs) are a key element of multimodal analgesia strategies, effectively relieving postoperative pain, reducing opioid consumption, and improving postoperative recovery [7]. Common PNBs used post-TKA include single-shot fascia iliaca, femoral nerve, and adductor canal blocks; however, these methods primarily alleviate anterior rather than posterior knee pain [10].

The posterior knee capsule is innervated by the sciatic nerve, its branches, and the obturator nerve branches. The tibial nerve distributes throughout the posterior knee capsule, while the obturator nerve's posterior branch overlaps with the tibial nerve, innervating the upper-inner knee capsule. The upper-outer posterior knee capsule is also innervated by the peroneal nerve and sciatic nerve branches [11, 12]. Therefore, posterior knee pain post-TKA is closely related to the sciatic nerve and its branches. Current nerve block techniques targeting the posterior knee capsule mainly include the subgluteal sciatic nerve, popliteal fossa sciatic nerve, and interspace between the popliteal artery and capsule of the posterior knee (iPACK) blocks [13, 14]. However, the popliteal fossa sciatic nerve block is located in the surgical field, while other techniques pose technical challenges and risk of vascular injury and nerve damage, [15–17] making them unsuitable for managing postoperative posterior knee pain post-TKA.

The parasacral ischial plane block (PIPB) is an improved technique for sciatic nerve block in the parasacral area, where a local anesthetic is injected between the fascia over the piriformis and the presacral fascia. This technique, performed away from the surgical site, serves as a fascial plane block, effectively blocking the sacral plexus and sciatic nerve without direct nerve engagement, [18, 19] making it suitable for managing posterior knee pain. Our previous research showed that the PIPB catheterization technique is reliable for blocking the sacral plexus and sciatic nerve and alleviating long-term pain post-TKA. However, it poses risks of catheter-related complications [20]. Standard local anesthetics typically provide relief for 7–15 h, with adjuvants such as dexamethasone and dexmedetomidine marginally extending this duration by a few hours [21, 22]. To avoid catheter-related complications while ensuring prolonged pain relief, a longer-acting local anesthetic is required.

Liposomal bupivacaine (LB), a novel, long-acting, sustained-release local anesthetic, is a derivative of bupivacaine encapsulated within multi-vesicular liposomes (Depofoam). DepoFoam particles comprise non-concentric multilayered lipid structures, enabling bupivacaine release over 72–96 h [23, 24]. Both 133 mg and 266 mg LB have been reported to achieve effective analgesic effects in femoral nerve block and local infiltration post-TKA [25, 26].

Currently, there are no reports on LB use and the specific dosages for TKA analgesia management via PIPB. This study aimed to evaluate the analgesic efficacy of different doses of liposomal bupivacaine injected into the PIPB and clarify its utility in postoperative analgesia.

Materials and methods

Study design

This single-center, double-blinded, randomized controlled study was approved by the Ethics Committee of Fujian Provincial Hospital (Approval No. K2023-09–007/02) and adhered to the principles of the Declaration of Helsinki. This study followed the Consolidated Standards of Reporting Trials guidelines (registration no. ChiCTR2400079606). All participants provided written informed consent.

Participants

This study was conducted at Fujian Provincial Hospital from January 5, 2024, to May 31, 2024, and included patients aged 18–80 scheduled for unilateral TKA. Inclusion criteria comprised American Society of Anesthesiologists (ASA) I-II class; body mass index between 18–30 kg/m^2; willingness to participate with signed informed consent; ability to walk 20 m independently; and normal sensation function in the distribution area of the sciatic nerve. Exclusion criteria encompassed preoperative opioid use, study medication allergies, inability to use or understand patient-controlled analgesia device, site infection at the nerve block puncture, uncertain surface anatomical landmarks, sciatic nerve lesions, coagulation disorders, or refusal to consent.

Randomization

This study employed variable block randomization using R-4.3.0 language software to generate 46 random number tables with block lengths of 4 or 6 and a random seed set at 20,230,830. Independent statistical personnel assigned codes to the trial protocol based on the generated random numbers (Group A: 133 mg LB, Group B: 266 mg LB). Randomization sequences were sealed in opaque envelopes sequentially numbered from 1 to 46. Participants were randomly assigned to Group A or B in the order of their entry into the study and based on the random number and grouping information in the envelopes (after selection based on the inclusion and exclusion criteria). Treatment allocation was non-selective, and random numbers remained unchanged throughout the trials.

Procedures

Participants fasted for 8 h preoperatively and received no analgesic medications. Intravenous access was established, and normal saline was infused in an anesthesia preparation room. Baseline measurements were taken for lower limb sensory function (using a 5 °C ice pack) and maximum voluntary isometric contraction (MVIC) during ankle dorsiflexion.

The trial was double-blinded. Syringes containing LB were concealed in opaque plastic bags, ensuring that both the patients and anesthesiologists were unaware of the contents. Third-party medical personnel prepared the drug packages to appear identical for both groups. Group A received 133 mg LB diluted in 0.9% normal saline to a total volume of 20 ml, while Group B received 266 mg LB to a total volume of 20 ml.

An experienced anesthesiologist performed the PIPB with all aseptic precautions, the PIPB procedure was consistent with our previously established methods [18–20]. A 2–5 MHz probe was used to position the frame on the deep side of the greater sciatic foramen. LB was administered between the piriformis and the presacral fascia.

All surgeries were performed under general anesthesia using standard techniques after PIPB. Induction was achieved with intravenous injection of propofol (2 mg/kg) and sufentanil (0.5 ug/kg), followed by rocuronium bromide (0.6 mg/kg) as a muscle relaxant. After tracheal intubation, mechanical ventilation was adjusted to maintain end-tidal carbon dioxide pressure at 35–45 mmHg and SpO_2 at 90–100%. Intravenous inhalation anesthesia (propofol, remifentanil, and sevoflurane) was continued to maintain bispectral index values between 40–60, preventing intraoperative awareness [27, 28]. To prevent postoperative nausea and vomiting, 10 mg metoclopramide was intravenously administered 30 min before the surgery ended [27].

According to the multimodal analgesia protocol, 1 g of acetaminophen and 400 mg of celecoxib were administered on the morning of surgery [8, 29]. All surgeries were performed by the same experienced orthopedic surgical team. Prior to the implantation of tibial and femoral prostheses, local infiltration anesthesia (300 mg ropivacaine, 0.3 mL epinephrine 1:1000, 10 mg morphine, and isotonic sodium chloride solution to 39.7 mL) was injected into the suprapatellar pouch, meniscus, and fat pad, excluding the posterior knee capsule [30–32].

Postoperatively, patients received routine analgesia; 1 g acetaminophen every 6 h and 200 mg celecoxib every 12 h [8, 29]. Additionally, a rescue intravenous analgesia pump was provided (2 ug/kg sufentanil and 20 mg tropisetron, diluted in normal saline to 100 ml) without a background dose. The pump was administered when requested by the patient with a Numerical Rating Scale (NRS) score ≥ 4, [33] with a single dose of 2 ml given through patient-controlled analgesia with a lockout time of 15 min.

Outcomes

Blinded data collectors recorded all relevant data. Postoperative knee pain peaks in the first few days, [26] and considering the duration of action of LB is 72 h, this research focused on evaluating its analgesic efficacy over 3 days. The primary outcome measure was the cumulative area under the curve (AUC) of the NRS scores for resting pain during the first 72 h post-surgery (NRS-AUC $R_{0\text{-}72\ h}$), assessed every 6 h from 0 to 72 h [25]. The NRS is an 11-point pain scale ranging from 0 (no pain) to 10 (worst pain), categorized as follows: 0 (no pain), 1–3 (mild pain), 4–6 (moderate pain), and 7–10 (severe pain) [26].

The formula for AUC calculation was as follows: [33]

$$AUC = \sum \frac{\left(NRS_i + NRS_j\right) \times \left(t_j - t_i\right)}{2}$$

where NRS_i and NRS_j represent NRS scores at postoperative hours i or j ($j > i$, $i = 0, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72$ h, $j = i + 6$). The NRS-AUC R/A_{time} is the AUC of the NRS at rest or during activity.

Secondary outcomes included the NRS scores during activity at various time points postoperatively, recorded every 6 h postoperatively for 72 h, and differentiated pain assessment between the anterior and posterior

aspects of the knee. Pain scores during activity were measured at maximum knee flexion [26]. The postoperative rescue analgesic consumption every 24 h, total rescue analgesic consumption, and the time of first rescue analgesic administration were also recorded. The consumption was converted to oral morphine equivalents (OME) [34].

Nerve block onset and regression were also observed. The onset time was determined based on decreases in sensation and motor function, while the regression time was determined based on sensation function recovery [35, 36]. Sensory block assessment was as follows: sensory function on the metatarsal, dorsal, and lateral sides of the calf were evaluated using a pinprick test or 5 °C ice pack test (0: normal sensation, 1: delayed sensation, 2: sensory loss). Measurements were taken every 5 min after PIPB, and sensory block onset was considered present if the score was ≥ 1 at any site. Repeated assessments were performed every 6 h postoperatively, with sensory block regression when the score was 0. Motor block assessment was as follows: motor function was based on the MVIC generated during ankle dorsiflexion [36] assessed using a dynamometer fixed on a wooden board attached to the ankle, with slow dorsiflexion required to achieve maximum force in 2 s, holding for 3 s, and then releasing. The MVIC for dorsiflexion of the ankle was measured in patients lying in the supine position. The foot was fixed to the dynamometer in a neutral position with a strap placed over the mid-foot and around the dynamometer handle. The strap was tightened with an allowance of up to 5-kg force before active muscle contraction. This allowance was subtracted from the maximal force development to obtain MVIC (Supplementary Fig. 1) [36]. Three consecutive assessments were performed with a 30-s interval between each assessment. To minimize potential random variability, the MVIC results were averaged [0, normal contraction; 1, weakened contraction (MVIC < 80% of baseline value); 2, no contraction (MVIC = 0)]. Measurements were taken every 5 min after the PIPB, with motor block onset considered when the score was ≥ 1.

Adverse events, including nausea, vomiting, drowsiness, constipation, fever, anxiety, sore throat, etc., were recorded [36]. Patient satisfaction with analgesia was assessed on the postoperative day (POD) 4 using a 5-point Likert scale (ranging from "very dissatisfied" to "very satisfied") [25]. Rehabilitation quality evaluation included measurements of the knee joint flexion angle (the flexion range of motion, ROM), [37] independent standing, walking capability, and time for ambulation with walker assessed on POD 4. The two-minute walking test was conducted at discharge [38]. The length of hospital stay was defined as the interval from admission to discharge. Discharge criteria comprised independent walking capability, NRS < 4, and absence of orthopedic complications [39].

Statistical analyses

Sample size was determined based on data from previous trials involving eight patients. The mean (standard deviation [SD]) of NRS-AUC $R_{0\text{-}72\ h}$ was 135 (24.74) and 117 (11.49) for Groups A and B, respectively. Sample size was calculated using a two-sample mean comparison t-test, with a two-sided $\alpha = 0.05$ and a power of $(1\text{-}\beta) = 0.80$. Each group was determined to require 20 patients. Considering a 10% dropout rate, 23 patients were needed per group, totaling at least 46 patients.

Microsoft Excel 2019 was used to establish the database, and SPSS software (version 25.0) was used for data analysis. The Shapiro–Wilk test for normality and Levene's test for homogeneity of variance were conducted for continuous variables. Data meeting these criteria are expressed as mean (SD) and compared using two-sample t-tests. Data not meeting the criteria are expressed as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies (percentages) and compared using Pearson's chi-square test or Fisher's exact test. Pain scores at various time points were compared using repeated-measures analysis of variance (ANOVA), with further simple analyses performed using the Mann–Whitney U test. Kaplan–Meier survival analysis described sensory and motor block onset and regression times in both groups, with comparisons conducted using the log-rank test. Statistical significance was set at $p < 0.05$.

Results

Among the 55 patients screened during the study period, eight were excluded for not meeting the inclusion criteria, and one declined to participate. Forty-six patients were finally enrolled and randomly assigned to groups A (n = 23) or B (n = 23). One patient in Group A was lost to follow-up and was not included in the data analysis (Fig. 1).

Baseline demographics did not differ significantly between the two groups (Table 1).

Our primary focus was the overall analgesic effect at rest during the first 3 postoperative days. The NRS-AUC $R_{0\text{-}72\ h}$ in Group A was 132.3 (19.7), significantly higher than 97.3 (19.1) in Group B (P = 0.001) (Fig. 2).

The overall analgesic effects were also assessed based on the NRS-AUC within 1–2 days postoperatively. Group A scored higher than Group B in terms of NRS-AUC

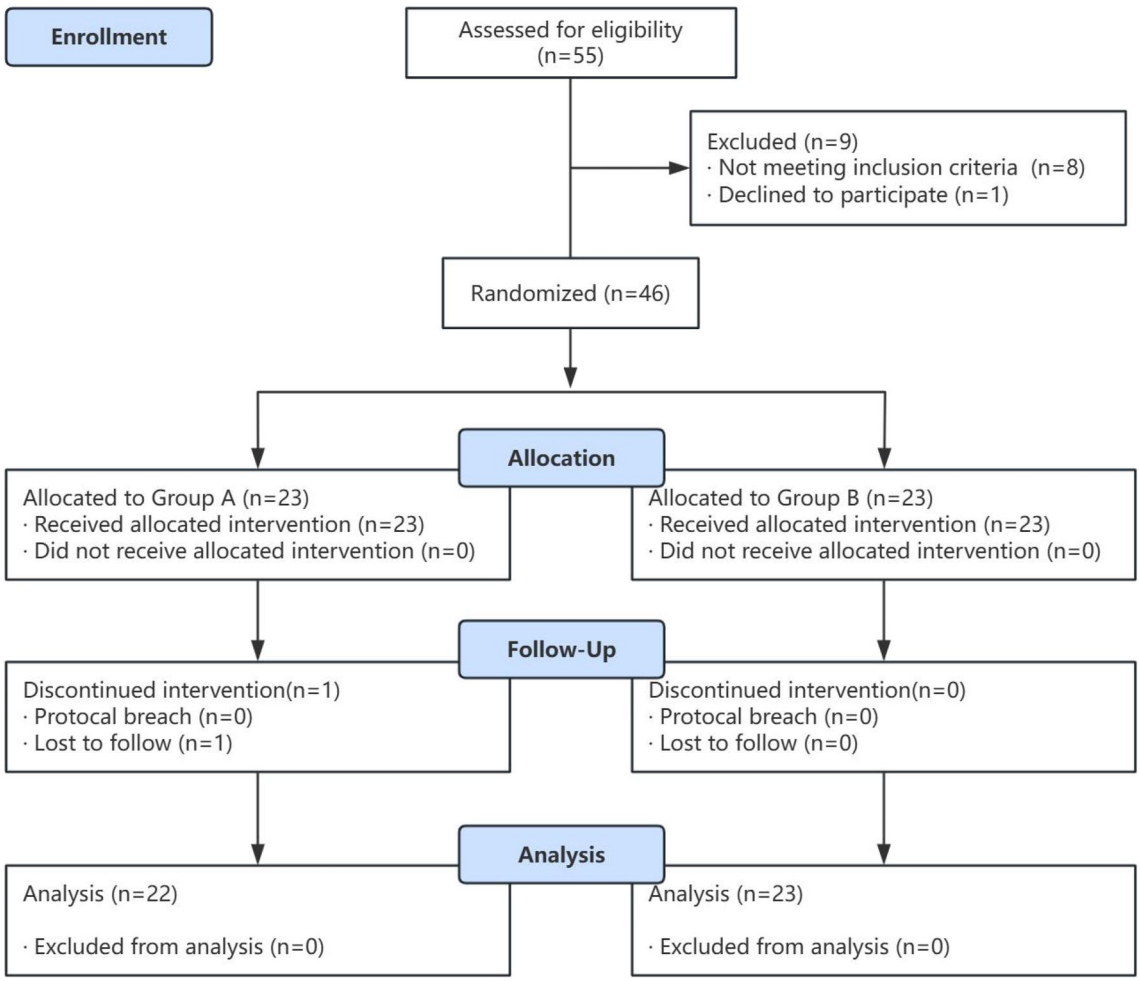

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram

$R_{0\text{-}24\ h}$ [47.5 (14.1) vs. 26.6 (11.1), p = 0.001], NRS-AUC $R_{0\text{-}48\ h}$ [115.6 (18.7) vs. 82.7 (15.8), p = 0.001] (Fig. 2).

Subsequently, the NRS-AUCs on each postoperative day were analyzed. Group A scored higher than Group B in terms of NRS-AUC $R_{0\text{-}24\ h}$ and NRS-AUC $R_{24\text{-}48\ h}$ [68.2 (12.8) vs. 56.1 (11.3), p = 0.002]. However, no significant difference was observed between the two groups on the third day regarding NRS-AUC $R_{48\text{-}72\ h}$ ($p > 0.05$) (Table 2).

A repeated-measures ANOVA on NRS scores at various time points at rest revealed a significant interaction between the factors of "group" and "time" ($p = 0.001$). A two-sample t-test conducted for "group," indicated significant between-group differences only at 12 h[difference(95%CI), 0.753(0.319, 1.187)], 18 h[difference(95%CI), 1.779(0.998, 2.559)] and 24 h [difference(95%CI), 1.696(1.095, 2.296)] postoperatively ($p < 0.05$) (Fig. 3).

For pain assessment during activity, the overall analgesic effects within 1, 2, and 3 days postoperatively were evaluated using NRS-AUC $A_{0\text{-}24\ h}$, NRS-AUC $A_{0\text{-}48\ h}$, NRS-AUC $A_{0\text{-}72\ h}$, which showed no statistically significant differences between the two groups. Subsequently, the analgesic effects each day during activity were assessed separately. No significant between-group differences were observed on the second and third days regarding NRS-AUC $A_{24\text{-}48\ h}$ and NRS-AUC $A_{48\text{-}72\ h}$ ($p > 0.05$).

Finally, repeated-measures ANOVA comparing the NRS scores at various time points during activity between the two groups indicated a significant interaction between the factors of "group" and "time" ($p = 0.010$). A simple two-sample *t*-test analysis on the "group" factor revealed no significant differences at any time point ($p > 0.05$) (Fig. 4).

A significant between-group difference in the rescue analgesic dosage was observed on the POD1 [difference(95%CI), 26.5(7.1, 46.0)] but not on POD 2 [$p = 0.107$], POD 3 [$p = 0.628$] or the total amount

Table 1 Baseline characteristics

	Group A (n = 22)	Group B (n = 23)	*p* value
Age, year	66.8 (4.4)	67.7 (5.9)	0.558
Height, cm	161.3 (6.9)	159.7 (6.4)	0.418
Weight, kg	64.3 (10.0)	61.7 (7.0)	0.323
Sex			0.999
Male	2 (9.1%)	3 (13.0%)	
Female	20 (90.9%)	20 (87.0%)	
ASA physical status			0.489
I	1 (4.5%)	0 (0.0%)	
II	21 (95.5%)	23 (100.0%)	
Surgical side			0.641
Left	9 (40.9%)	11 (47.8%)	
Right	13 (59.1%)	12 (52.2%)	
Duration of the surgery	108.4 (10.7)	112.2 (13.8)	0.314
Length of hospital, day	5 (4, 5)*	5 (4, 5)	0.334

ASA, American Society of Anesthesiologists

Values are presented as mean(SD), median(IQR), or number(proportion)

*One patient had prolonged hospital stay due to wound infection and was not included in the data, n = 20

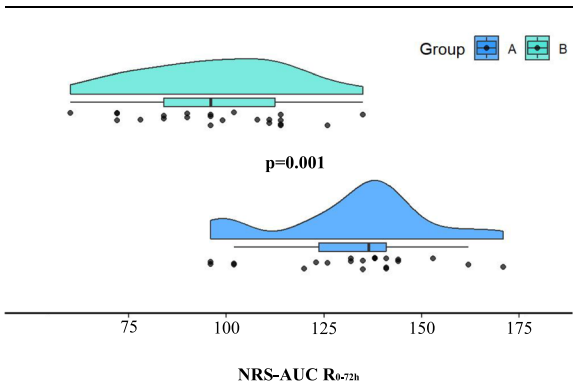

Fig. 2 Primary outcome: the NRS-AUC at rest during 0–72 h after Total Knee Arthroplasty

[$p = 0.563$]. The time of first rescue analgesia use was significantly shorter in Group A than Group B [12.5 vs. 16.0, $p = 0.004$] (Table 2).

Onset and regression of the PIPB, the onset and regression times of the LB were evaluated based on both sensory and motor functions. The onset time of PIPB was defined as a sensory function score of 1, with an onset time of 60 and 35 min for Group A and B, respectively ($p < 0.0001$) (Fig. 5), and a motor function score of 1, with an onset time of 85 and 50 min for Group A and Group B, respectively ($p < 0.0001$) (Fig. 6). Onset time was earlier for sensory than motor block in both groups ($p < 0.001$) (Table 2). The regression time of PIPB was defined as a sensory score of 0, with regression times of 36 and 48 h for the two groups; however, no significant between-group difference was observed ($p = 0.280$) (Table 2).

Adverse events and rehabilitation quality did not differ between the two groups. (Table 3).

Discussion

From the perspective of innervation of the knee joint capsule, the anterior capsule is primarily innervated by the femoral nerve and its branches, [11] while the posterior capsule is majorly innervated by the sciatic nerve and its branches [12]. Therefore, posterior knee pain is closely associated with the sciatic nerve. The PIPB is a modified parasacral sciatic nerve block technique. A local anesthetic is administered into the interspace between the piriformis fascia and the presacral fascia. The anesthetic agent disseminates throughout the fascial compartment, effectively inhibiting the sacral plexus and the sciatic nerve located within this region [18, 19]. Historically, the transgluteal approaches for sacral plexus or sciatic nerve blocks have experienced limited adoption due to the deep anatomical positioning of the nerves and inadequate tissue visualization, which increased the risk of unintentional neural and vascular injuries. The PIPB, as a fascial plane technique, avoids direct needle-to-nerve contact, thereby minimizing risks of neural and vascular injury. Continuous PIPB has demonstrated efficacy in providing postoperative analgesia following TKA, exhibiting a high safety profile and exerting minor effects on motor function [20].

This is the first reported study to use LB in PIPB. Previous studies could not ensure the stability of the bupivacaine concentration released by LB, [24] Therefore, it was essential to determine whether it effectively provided postoperative analgesia to the posterior knee joint post-TKA through PIPB. This study focused on the overall postoperative analgesic effect over the first 3 days by observing the AUC of the NRS from 0 to 72 h, avoiding biases from relying on a single time point analysis. NRS score = 4 is usually the minimal threshold for rescue analgesia in moderate to severe pain, [33, 40] thus, NRS score ≤ 3 is considered tolerable.[41] Therefore, NRS-AUC $_{0\text{-}72\ h} = 216$ was established as the standard value in this research, indicating that analgesia below the standard is effective. These findings indicated that both groups experienced effective pain relief at rest, however, efficacy varied: the AUC-$NRS_{0\text{-}72\ h}$ at rest was 132.3 (19.7) and 97.3 (19.1) for Group A and B, respectively ($p < 0.05$), with a significantly better analgesic effect observed for the 266 mg dose.

Additionally, the analgesic effect of 266 mg LB on POD 1, 2, and 3 was superior to that of 133 mg LB. This

Table 2 Summary of Results from Other Efficacy Assessments

Variables	Group A (n = 22)	Group B (n = 23)	*p* value
NRS-AUC			
NRS-AUC R $_{0\text{-}72\ h}$	132.3	97.3	0.001*
NRS-AUC R $_{0\text{-}24\ h}$	47.5 (14.1)	26.6 (11.1)	0.001*
NRS-AUC R $_{0\text{-}48\ h}$	115.6 (18.7)	82.7 (15.8)	0.001*
NRS-AUC R $_{24\text{-}48\ h}$	68.2 (12.8)	56.1 (11.3)	0.002*
NRS-AUC R $_{48\text{-}72\ h}$	16.6 (8.1)	14.6(9.7)	0.450
NRS-AUC A $_{0\text{-}24\ h}$	148.5 (114.0–162.0 [45.0–171.0]) †	132.0 (99.0–159.0 [33.0–192.0])	0.413
NRS-AUC A $_{0\text{-}48\ h}$	339.0 (298.5–366.8 [252.0–399.0])	333 (306–360 [180.0–339.0])†	0.557
NRS-AUC A $_{0\text{-}72\ h}$	484.0 (54.2)	474.9 (73.6)	0.642
NRS-AUC A $_{24\text{-}48\ h}$	201.0 (174.0–217.5 [150.0–234.0])	198 (189.0–213.0 [147.0–231.0])†	0.891
NRS-AUC A $_{48\text{-}72\ h}$	150.9 (32.1)	151.0 (26.6)	0.992
OME, mg			
Total	108.4 (52.6–154.9 [22.1–224.4])	107.8 (81.2–122.9 [0.0–156.2])†	0.563
POD 1	43.1 (24.1–60.9 [0.0–190.1])†	27.2 (5.4–41.0 [0.0–54.6])	0.009*
POD 2	52.3 (26.7)	40.7 (20.3)	0.107
POD 3	6.0(0.0–11.0[0.0–29.6])†	5.1 (0.0–9.1[0.0–21.8]) †	0.628
Primary pain site			0.022*
Anterior knee	15 (68.2%)	22 (95.7%)	
Posterior knee	7 (31.8%)	1 (4.3%)	
Time to first rescue analgesic, h	12.5 (11.0–16.0 [8.0–25.0])†	16.0 (14.0–19.3 [11.0–27.0])‡	0.004*
Satisfaction with analgesia	5 (4.8–5[3, 5]) †	5 (5–5[4, 5])†	0.348
Onset time, min			
Sensory block	60	35	< 0.001*
Motor block	85	50	< 0.001*
Regression time, h			
Sensory block	36	48	0.280

NRS: numerical rating scale score; AUC: the cumulative area under the curve; NRS-AUC: the AUC of NRS; NRS-AUC R/A $_{time}$: the AUC of NRS at rest or activity during times; OME, oral morphine equivalents

Values are number (proportion), mean (SD) or median (IQR [range])

*Denotes statistical significance ($p < 0.05$); † data is skewed; ‡ one patient did not receive rescue analgesia, n = 22

contrasts with studies by Hadzic et al. [25] and Bramlett et al. [26] They respectively used LB for postoperative analgesia in TKA through femoral nerve block and local infiltration and found no significant differences in AUC-NRS between the two groups at rest and activity. The possible reasons for this include the fact that the sciatic nerve is the largest in the human body, [42] and the amount of bupivacaine released by 133 mg LB may have been insufficient for complete blockade at certain time points,[43] whereas the bupivacaine released by 266 mg LB provided an adequate dose. Additionally, differences in analgesic regimens may account for the varied results.

Given the differences in analgesic scores, further analysis of analgesic efficacy for each day and time point revealed a significant between-group difference in analgesic effects on PODs 1 and 2 but not on POD 3 (Table 2).

For a single time point, the minimal clinically important difference of NRS postoperative pain 1.0–1.5 and 10mg OME has been reported [44–46]. This study found statistical significance in the NRS of the two groups only at 12, 18 and 24 h after surgery, and the difference of NRS was greater than 1.5 only at 18 and 24 h after surgery. Correspondingly, Group A showed significantly higher OME on POD 1(difference, 26.5mg) and earlier time to first rescue analgesia compared to Group B

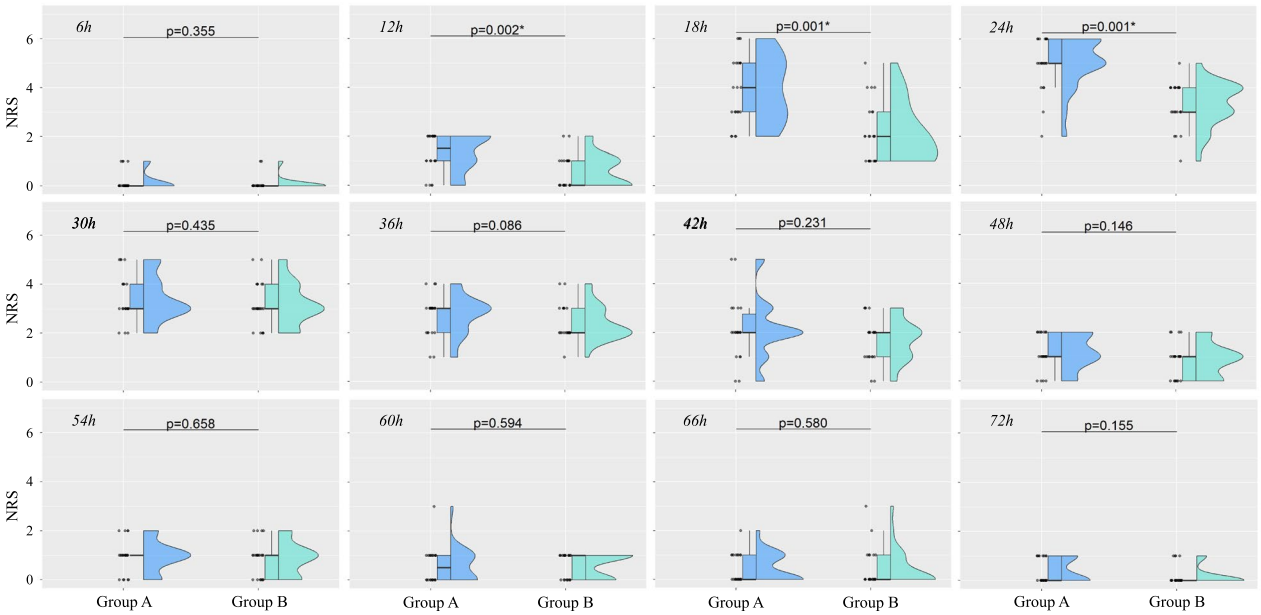

Fig. 3 NRS scores at various time points during 0–72 h when the patient was at rest

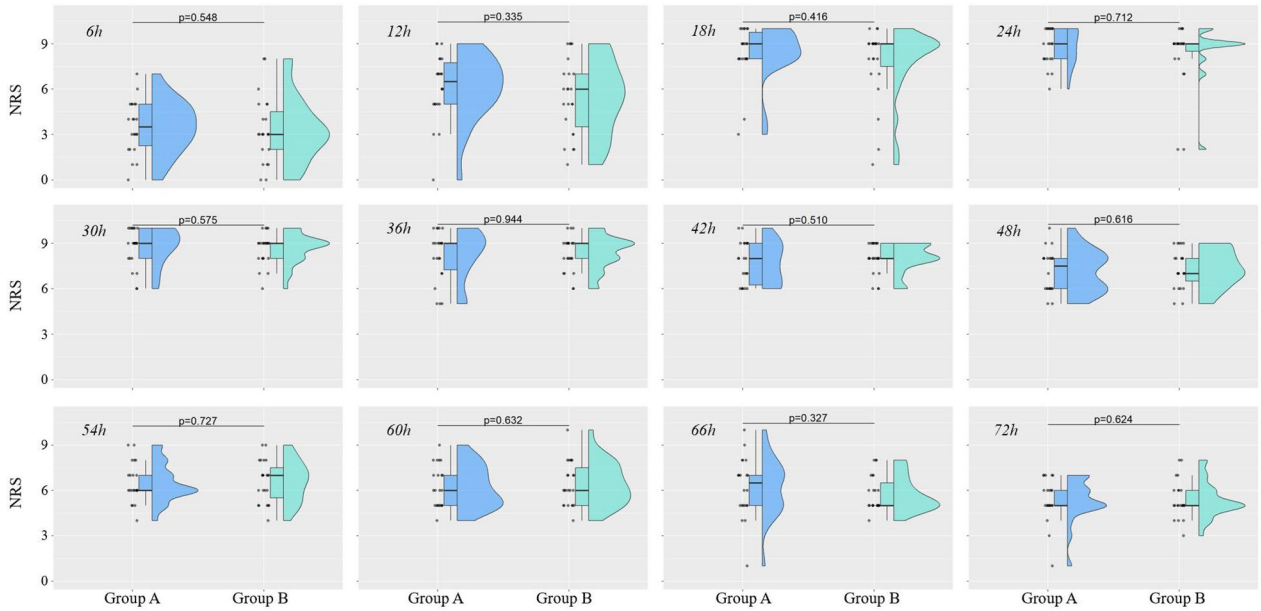

Fig. 4 NRS scores at various time points during 0–72 h when the patient was active (maximum knee flexion)

(both $p < 0.05$). The results indicated a superior analgesic effect of 266 mg LB compared with 133 mg LB POD 1. This phenomenon may be related to the second peak in LB blood concentration at 12–36 h post-administration. Due to the low dose of 133 mg LB, even if a second peak release occurs, it may not meet the analgesic demands, whereas bupivacaine released by 266 mg LB can provide better analgesic effects [24].

The pain score research defined as when the patient maximally flexes the knee as the NRS score during activity. Our results indicated no significant between-group difference in NRS-AUC scores during activity on PODs 1, 2, and 3. Further single-point analysis

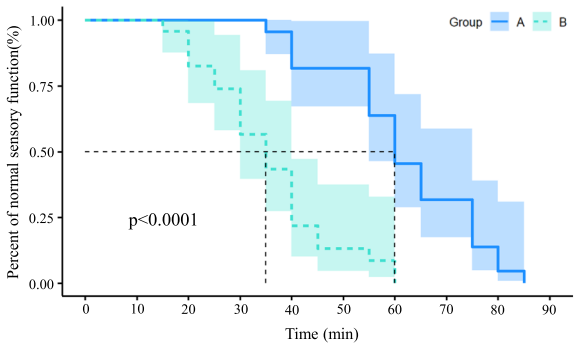

Fig. 5 Kaplan–Meier curve for the sensation function regression time after the Parasacral Ischial Plane Block

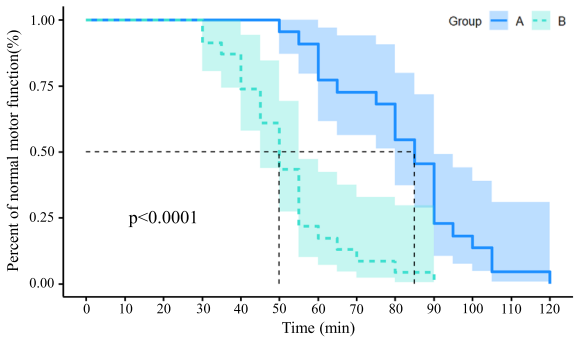

Fig. 6 Kaplan–Meier curve for the motor function regression time after the Parasacral Ischial Plane Block

Table 3 Rehabilitation quality and adverse events

	Group A (n = 22)	Group B (n = 23)	*p* value
Rehabilitation quality			
ROM, angle	107.1 (8.8)	104.1 (8.6)	0.252
Ability to stand up	22 (100%)	23 (100%)	0.999
2 min walking test, meter	36.3 (7.6)	33.5 (7.3)	0.221
Time for ambulation with walker, hours	8.7 (0.6)	8.3 (0.8)	0.076
Adverse events			
Nausea	9 (40.9)	5 (21.7)	0.165
Vomiting	4 (18.2)	2 (8.7)	0.619
Dizziness	4 (18.2)	2 (8.7)	0.619
Fever	1 (4.5)	1 (4.3)	0.999
Wound infection	1 (4.5)	0 (0.0)	0.489
Constipation	4 (18.2)	2 (8.7)	0.619
Drowsiness	5 (22.7)	7 (30.4)	0.559
Anxiety	5 (22.7)	5 (21.7)	0.999
Pruritus	0 (0)	0 (0)	0.999
Insomnia	8 (36.3)	2 (8.6)	0.061
Loss of appetite	6 (27.3)	4 (17.4)	0.661
Sore throat	2 (9.1)	1 (4.3)	0.968
Back pain	6 (27.3)	7 (30.4)	0.815
Fall	0 (0.0)	0 (0.0)	0.999
Swelling of the knee	7 (31.8)	6 (26.1)	0.672

ROM, knee joint range of motion

Values are number (proportion)

revealed no difference in the NRS scores between the two groups. We concluded that both LB doses are relatively ineffective in alleviating pain during knee activity, consistent with LB's effect on TKA when performing femoral nerve block [25]. Rehabilitation training following TKA is typically recommended within 1–2 days postoperatively [47]. However, the conclusion may not support the beneficial effects of LB on pain relief during activity.

Drug sustained-release technology potentially affects the time required to reach peak drug concentration [23]. As there are no reports on the onset time of LB in PIPB, we used sensory and motor assessments in the sciatic nerve distribution area to define LB's onset time [35, 36]. The sensory assessment points included the lateral aspect of the foot, dorsum of the foot, and lateral aspect of the lower leg, with onset defined as when the sensory score at any site reached 1. Contrastingly, the motor assessment mainly focused on ankle dorsiflexion. Previous research on motor assessment abandoned the subjective methods of the Bromage Score [48] and Lovett scale score [49] and instead used "the MVIC of ankle dorsiflexion" as the indicator for motor assessment. A 20% decrease in MVIC compared to baseline was confirmed as the onset of motor block. This method can accurately assess the effect of nerve block, which is more objective than the patients' subjective feelings or other indicators. Additionally, MVIC provides quantitative values, which are more suitable for comparing changes in muscle strength, facilitating rapid assessment of PIPB effectiveness [50]. Using MVIC as a measure for PIPB regression in TKA patients may introduce bias due to factors such as bandaging and pain influencing MVIC. Therefore, sensory indicators alone were utilized to assess PIPB regression, with sensory block regression defined as a score return to zero.

When sensory assessment was used to determine LB onset in the PIPB, Group A was 60 min, while Group B was 35 min, indicating a significantly later onset time in Group A. When the MVIC was used to assess LB onset, Group A was 85 min, and Group B was 50 min. However, whether based on sensory or MVIC assessment, it appears that the onset time of LB is significantly longer than that of bupivacaine [43]. A similar phenomena has been observed in the brachial plexus block, where LB exhibits a shorter onset time and longer duration, likely due to the smaller size of the brachial plexus compared

to the sciatic nerve [51]. We also observed that the sensory onset time in both groups preceded the motor onset time, similar to bupivacaine [43]. This may be due to the finer sensory nerve fibers [52] and the higher sensitivity of amide-type anesthetics to sensory nerve fibers [53]. Duration of sensory block regression showed no significant between-groups difference ($p > 0.05$), suggesting a potential correlation with the decreased concentration of bupivacaine released by LB.

LB absorption into the bloodstream shows uneven patterns, indicating non-constant release rates, leading to inconsistent block effects [24, 54]. A patient in this study, who received 20 ml of 266 mg LB, showed sensory and motor function recovery at 24 h postoperatively but experienced numbness and limb movement disorders in the lower limbs again at 48 h postoperatively, with complete recovery at 90 h. During this period, the patient's pain scores significantly decreased, allowing mobilization on the 5th day without experiencing sensory or motor abnormalities. This case mirrors findings reported by Discepola et al. [55] where a patient experienced the "re-block" phenomenon, with the effect of the block gradually disappearing about 12 h after the block, and the patient woke up with numbness in the lower limbs again the next morning post-surgery. Excessive and abnormal nerve deposition may prolong block duration, [24] suggesting that higher LB doses could induce secondary block-related effects, such as sensory deficits and walking instability.

Rehabilitation quality did not differ significantly between groups. The incidence rates of adverse events in both groups were similar, mainly entailing nausea, vomiting, drowsiness, and anxiety, which is consistent with other studies [25, 26]. No direct evidence implicates LB use as the cause of these adverse reactions, affirming the safety of administering 266 mg LB via PIPB.

The rationale for conducting assessments every 6 h during the 0–72 h postoperative period is based on the following considerations: First, postoperative pain following TKA is typically most severe within the first three days, during which early rehabilitation training is recommended [47]. Frequent rehabilitation and physical therapy exercises during this critical period necessitate close monitoring of pain levels to optimize analgesic management for both patients and surgeons. Secondly, given that this is the inaugural study to employ LB in the context of PIPB, a comprehensive assessment of sensory and motor recovery patterns was necessary to evaluate the prolonged analgesic effects of LB over a 72-h period. Shorter assessment intervals were essential to capture these pharmacodynamic characteristics [24]. Therefore, based on prior research, [56–59] we conducted postoperative follow-up assessments every 6 h.

This study had several limitations. First, there was insufficient investigation into other LB doses, primarily due to safety and economic feasibility considerations in clinical applications. Furthermore, the reference doses widely used in clinical studies are mainly 133 mg and 266 mg. Future studies should explore other doses. Second, LB in PIPB can lead to lower limb muscle strength changes, requiring good patient compliance to prevent adverse events such as falls. Third, comparative studies on the same type of amide local anesthetic, bupivacaine are needed. Fourth, this study assessed only short-term rehabilitation quality until discharge and did not evaluate long-term rehabilitation quality due to loss of follow-up. This study was a single-center, randomized controlled trial, and multicenter trials with larger cohorts are required to validate these findings.

These findings revealed that 266 mg LB offered superior pain relief for patients on POD 3 at rest, but did not meet the analgesic needs during activity, with no significant between-group differences observed.

Abbreviations

LB	Liposomal bupivacaine
TKA	Total knee arthroplasty
PIPB	Parasacral ischial plane block
AUC	The cumulative area under the curve
NRS	The Numerical Rating Scale
PNBs	Peripheral nerve blocks
iPACK	The popliteal artery and capsule of the posterior knee
ASA	American Society of Anesthesiologists
MVIC	Maximum voluntary isometric contraction
NRS-AUC R/A	The cumulative area under the curve of the NRS at rest or during activity
OME	Oral morphine equivalents
POD	Postoperative day
SD	Standard deviation
IQR	Interquartile range
ANOVA	Repeated-measures analysis of variance

Supplementary Information

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Supplementary material 1: The MVIC measurement of ankle dorsiflexion

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Author's contributions

Xuan Pan: Conceptualization, Methodology, Investigation, Writing—Original Draft. Peng Ye: Formal analysis, Writing—Review & Editing. Ting Zheng: Methodology, Funding acquisition. Cansheng Gong: Investigation. Chunying Zheng: Resources, Project administration, Funding acquisition. Xiaochun Zheng: Project administration, Supervision, Funding acquisition.

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Availability of data and materials
Data are available depending on the request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Fujian Provincial Hospital (Approval No. K2023-09–007/02) and adhered to the principles of the Declaration of Helsinki.

Consent for publication
Informed consent was obtained from all individual participants included in the study.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anaesthesiology, Fujian Provincial Hospital, Shengli Clinical Medical College of Fujian Medical University, 134 Dongjie, Fuzhou 350001, Fujian, China. [2]Fujian Provincial Key Laboratory of Emergency Medicine, Fujian Provincial Key Laboratory of Critical Care Medicine, Fujian Emergency Medical Center, Fujian Provincial Co-Constructed Laboratory of "Belt and Road", Fuzhou, China.

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