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CLINICAL TRIAL REPORT

Esketamine as an Adjuvant to Ropivacaine in Genicular Nerve and IPACK Blocks for Total Knee Arthroplasty: A Double-Blind Randomized Trial

Xiaona Zhu[1], Wanli Bao[2], Lu Wang[3], Lvdan Huang[1], Quanguang Wang[1,*], Linmin Pan[1,*]

[1]Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [2]Department of Anesthesiology, The People's Hospital of Wencheng, Wenzhou, Zhejiang, People's Republic of China; [3]Department of Joint Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Linmin Pan; Quanguang Wang, Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China, Tel +86-150-6846-8153; +86-137-3693-5500, Email panlinmin@wmu.edu.cn; quanguangwang@wzhospital.cn

Purpose: Chronic postsurgical pain (CPSP) following total knee arthroplasty (TKA) affects up to 44% of patients and markedly impairs recovery and quality of life. Although regional anesthesia is integral to multimodal analgesia, its preventive effect on CPSP remains limited. Esketamine, a potent N-methyl-D-aspartate receptor antagonist with analgesic and neuroprotective properties, may enhance local anesthetic efficacy and reduce the development of chronic pain.

Patients and Methods: In this prospective, randomized, double-blind trial, 367 patients undergoing unilateral TKA under general anesthesia with peripheral nerve blocks were allocated to three groups: CTRL (normal saline), ROP (0.5% ropivacaine), and ESK (0.5% ropivacaine plus esketamine 0.2 mg/kg) for genicular nerve and IPACK blocks. The primary outcome was the incidence of CPSP (Numerical Rating Scale ≥ 4) at 6 months. Secondary outcomes included opioid consumption, NRS pain scores, Timed Up and Go (TUG) test, walking distance, Quality of Recovery-15 (QoR-15) scores, and adverse events.

Results: At 6 months, the incidence of CPSP was significantly lower in the ESK group (4.9%) than in the ROP (17.9%) and CTRL (27.0%) groups. Esketamine significantly reduced overall pain burden (AUC = 559.3 ± 59.0 vs 641.9 ± 55.8 and 679.2 ± 58.5; $P < 0.0001$). It also lowered 24-hour opioid consumption, with patients in the ESK group requiring less morphine equivalent (26.8 ± 11.5 mg) compared with the ROP (29.7 ± 11.8 mg) and CTRL (34.8 ± 11.9 mg) groups ($P < 0.001$). Functional recovery improved, with shorter TUG times, longer walking distance, and higher QoR-15 scores. No serious adverse events or psychomimetic reactions were reported.

Conclusion: Esketamine as an adjuvant to ropivacaine in genicular and IPACK blocks significantly reduced CPSP incidence and improved early functional recovery after TKA without increasing adverse effects. Perineural esketamine may represent a safe and effective strategy to prevent pain chronification.

Keywords: chronic postoperative pain, esketamine, peripheral nerve block, IPACK block, total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is a widely practiced and secure operation generally carried out to ease symptoms in patients with advanced knee osteoarthritis.[1] The volume of TKAs performed worldwide has increased markedly in recent years, reflecting both an aging population and expanding surgical indications.[2] However, chronic postsurgical pain (CPSP) occurs in 10% to 50% of cases, with 2% to 10% of patients experiencing severe, long-lasting pain following surgery.[3] Studies have shown that the incidence of chronic pain following TKA is relatively high and correlates with various factors including preoperative pain, psychological status, and postoperative complications.[4] Although multimodal analgesia strategies—such as oral non-opioid medications, periarticular infiltration, and peripheral nerve blocks—have improved acute postoperative pain control, their effectiveness in preventing CPSP remains limited.[5]

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Adequate postoperative analgesia after TKA should not only ensure effective pain relief but also preserve lower limb motor strength, facilitating early rehabilitation and enhanced recovery.[6] Motor-sparing regional anesthesia techniques, such as the genicular nerve block (GNB) and the infiltration between the popliteal artery and the capsule of the knee (IPACK), selectively target sensory innervation to the anterior and posterior aspects of the knee, respectively.[7] These techniques enable early ambulation and functional recovery,[8] although their long-term impact on CPSP remains uncertain.[9]

Esketamine, the S-enantiomer of ketamine, is a potent N-methyl-D-aspartate (NMDA) receptor antagonist with additional interactions at opioid, monoaminergic, muscarinic, and voltage-gated ion channels.[10] When administered peripherally with local anesthetics, esketamine may extend block duration, attenuate rebound pain, and reduce central sensitization in non-intubated video-assisted thoracic surgery.[11] Its neuroprotective[12] and antidepressant effects[13] may offer added benefit, particularly in patients with psychological risk factors for CPSP.

To date, although esketamine has been studied in systemic use after hip and knee arthroplasty,[14] the effect of esketamine as an adjuvant in regional blocks targeting both anterior and posterior articular nerves of the knee has not been fully elucidated. We therefore conducted a prospective, randomized, double-blind trial to assess whether the addition of esketamine to ropivacaine for GNB and IPACK blocks could reduce the incidence of CPSP at 6 months following TKA. We hypothesized that the addition of esketamine to ropivacaine in peripheral nerve blocks would enhance perioperative analgesia, promote early functional recovery, and reduce the incidence of chronic postsurgical pain after TKA.

Materials and Methods

Study Design and Ethics

This single-center, prospective, randomized, double-blind controlled trial was conducted at the First Affiliated Hospital of Wenzhou Medical University. The study protocol was reviewed and approved by the institutional ethics committee (Approval No. KY2023-097) and was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2300073520). Written informed consent was obtained from all participants prior to enrollment. Patient recruitment began on September 9, 2023, and the study was completed on October 12, 2025. The trial was conducted in accordance with the Declaration of Helsinki principles and adhered to Standards of Good Clinical Practice.

Participants

Inclusion criteria: age 18–90 years; American Society of Anesthesiologists (ASA) physical status I–III; body mass index (BMI) between 18 and 40 kg/m^2; and scheduled for elective unilateral total knee arthroplasty (TKA) under general combined with spinal anesthesia. Exclusion criteria included: contraindications to spinal anesthesia or peripheral nerve blocks; history of prior knee trauma or surgery; neurological or psychiatric disorders affecting pain assessment; known allergy to study medications; chronic opioid use (≥30 mg oral morphine equivalents per day for ≥4 weeks); and uncontrolled hypertension or hyperthyroidism.

Randomization and Blinding

Participants were randomly assigned in a 1:1:1 ratio to one of three study groups using a computer-generated randomization sequence created with R software (version 4.2.2), employing a fixed block size of six. The sequence was prepared by an independent statistician. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes opened immediately prior to the intervention by a study nurse not involved in outcome assessment or data analysis. Both participants and investigators responsible for postoperative care and data analysis were blinded to group allocation. The anesthesiologist performing the nerve blocks was not involved in outcome assessment or further clinical management.

Anesthesia Protocol

All patients received standard intraoperative monitoring and premedication with 1–2 mg of midazolam intravenously. Spinal anesthesia was performed in the lateral decubitus position using a standard midline approach at the L3–L5 interspace, with 10–12.5 mg of 0.5% isobaric ropivacaine (Naropin®, AstraZeneca AB, Södertälje, Sweden) administered intrathecally. Following confirmation of adequate sensory blockade from spinal anesthesia, patients were positioned supine with the hip externally rotated and the knee slightly flexed. Ultrasound-guided nerve blocks were performed preemptively, before induction of general anesthesia. A high-frequency linear ultrasound probe (SonoSite X-Porte, SonoSite Inc., Bothell, WA, USA) was used to visualize target anatomical structures under sterile conditions.

A combined genicular nerve block (GNB),[15] targeting the superomedial, superolateral, and inferomedial genicular nerves, and an infiltration between the popliteal artery and the capsule of the knee (IPACK) block[16] were performed under real-time ultrasound guidance.

Patients were randomly assigned to one of three groups.

- Control group (CTRL): Patients received sham blocks with 0.9% normal saline under ultrasound guidance at the same anatomical sites and volumes as the active groups (GNB: 5 mL × 3 sites, total 15 mL; IPACK: 20 mL).
- Ropivacaine group (ROP): Patients received 0.5% ropivacaine with identical injection sites and volumes under ultrasound guidance.
- Esketamine group (ESK): Patients received a mixture of 0.5% ropivacaine and esketamine (0.2 mg/kg, Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China) using the same injection sites and volumes.

All nerve blocks were performed under real-time ultrasound guidance by the same experienced anesthesiologist who was not involved in postoperative evaluation. Blinding was maintained for both patients and assessors. After completion of the nerve block procedure, anesthesia was maintained with a laryngeal mask airway under general anesthesia, using propofol 2 mg/kg (Fresenius Kabi Deutschland GmbH, Graz, Austria), sufentanil 0.2 μg/kg (Humanwell Healthcare Co., Ltd., Wuhan, China), and rocuronium 0.6 mg/kg (Emeishan Tonghui Pharmaceutical Co., Ltd., Sichuan, China), and maintained with 1% sevoflurane (Sevorane®, AbbVie Inc., North Chicago, IL, USA) to achieve an adequate depth of anesthesia, keep bispectral index (BIS) values between 40 and 60.

Surgical Procedure

All procedures were performed under aseptic conditions. After anesthesia, a medial parapatellar incision was made to expose the joint, the patella was gently displaced laterally, and the medial meniscotibial ligament was transected to induce joint instability. The infrapatellar fat pad was preserved in all cases, with only minimal retraction when necessary. After confirming adequate destabilization, the joint was irrigated, the patella repositioned, and the wound closed in layers, followed by routine postoperative care.

Postoperative Analgesia

Postoperative analgesia was administered via patient-controlled intravenous analgesia (PCIA) with sufentanil (0.5 μg/mL), delivered through a programmable infusion pump (ZZB-1, Apon Medical Technology Co., Ltd., Jiangsu, China). The PCIA settings included a 3 mL bolus, a 15-minute lockout interval, a maximum dose of 10μg/hour, and a total reservoir volume of 200 mL.

All patients also received scheduled multimodal analgesia as part of standard perioperative care, which included oral acetaminophen 500–1000 mg every 6–8 hours (Tylenol®, Shanghai Johnson & Johnson Pharmaceuticals, Ltd., Shanghai, China) and a nonsteroidal anti-inflammatory drug (NSAID) such as celecoxib (Celebrex®, Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico, USA; 200 mg twice daily) or loxoprofen (Hunan Jiudian Pharmaceutical Co., Ltd., Changsha, China; 60 mg three times daily), unless contraindicated. Intravenous parecoxib 40 mg (Qilu Pharmaceutical Hainan Co., Ltd., Hainan, China) was permitted as rescue analgesia for breakthrough pain. Any additional opioid use was documented and converted to intravenous morphine equivalents for analysis.

Outcomes

The primary outcome was the presence or absence of CPSP,[17] defined as a numerical rating scale (NRS) score ≥ 4at rest or during movement at 6 months postoperatively.

Secondary outcomes included:

- Cumulative opioid consumption within 24 hours postoperatively, expressed as intravenous morphine equivalents (all analgesic agents were converted to IV morphine equivalents for standardized comparison).
- NRS pain scores were recorded at rest and during movement preoperatively, on postoperative days 1, 3, 7, and 14, and monthly from 1 to 6 months.
- Functional recovery, including Timed Up and Go (TUG) test and walking distance at 24 hours postoperative and preoperative.
- Quality of Recovery-15 (QoR-15) scores[18] were assessed preoperatively and at 24 hours postoperatively.
- Adverse events include dizziness, nausea and vomiting, hypotension, hypertension, urinary retention, and signs of local anesthetic systemic toxicity.

Sample Size Calculation

The required sample size was calculated using PASS software version 15.0 (NCSS, Kaysville, UT, USA). The primary comparison was ESK vs ROP for the 6-month CPSP rate, assumed at 2% vs 14% from pilot data. Using a two-sided $\alpha = 0.0167$ (Bonferroni adjustment for three pairwise tests) and 80% power for a two-sample comparison of proportions (chi-square test), the required size was 106 patients per group. Allowing 15% attrition, we planned to enroll 124 per group.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation (SD) and were compared using one-way analysis of variance (ANOVA) followed by Tukey post hoc tests. Non-normally distributed data are reported as median with interquartile range (IQR) and compared using the Kruskal–Wallis test. Categorical variables are expressed as counts (percentages) and were analyzed using the chi-square test. When significant interactions were detected, post hoc pairwise comparisons were performed using Sidak's adjustment. A multivariate logistic regression analysis was performed to adjust for potential confounding factors of chronic postsurgical pain. A two-tailed $P< 0.05$ was considered statistically significant.

Results

A total of 390 patients scheduled for elective unilateral total knee arthroplasty (TKA) were assessed for eligibility. Of these, 13 patients were excluded due to failure to meet inclusion criteria (eg, preexisting neuropathy, psychiatric illness, or chronic opioid use), and 5 declined to participate. The remaining 372 patients were randomly assigned in equal numbers to one of three groups (n=124).

During the study, Five patients were excluded from the final analysis: one due to protocol deviations (block failure), two due to early discharge prior to completing the 48-hour postoperative evaluation, and two due to withdrawal of consent. Consequently, data from 367 patients were included in the final analysis (n = 122 in the CTRL group, n = 123 in the ROP group, and n = 122 in the ESK group) (Figure 1).

Baseline demographic and perioperative characteristics were comparable among the three groups. In addition, a multivariate logistic regression analysis was performed to adjust for potential confounding factors. After controlling for age, sex, BMI, body weight, height, ASA class, operative side, and operative duration, only group allocation and preoperative pain scores remained independently associated with the incidence of chronic postsurgical pain at 6 months. None of the baseline demographic or perioperative variables showed a significant independent effect on CPSP. (Table 1).

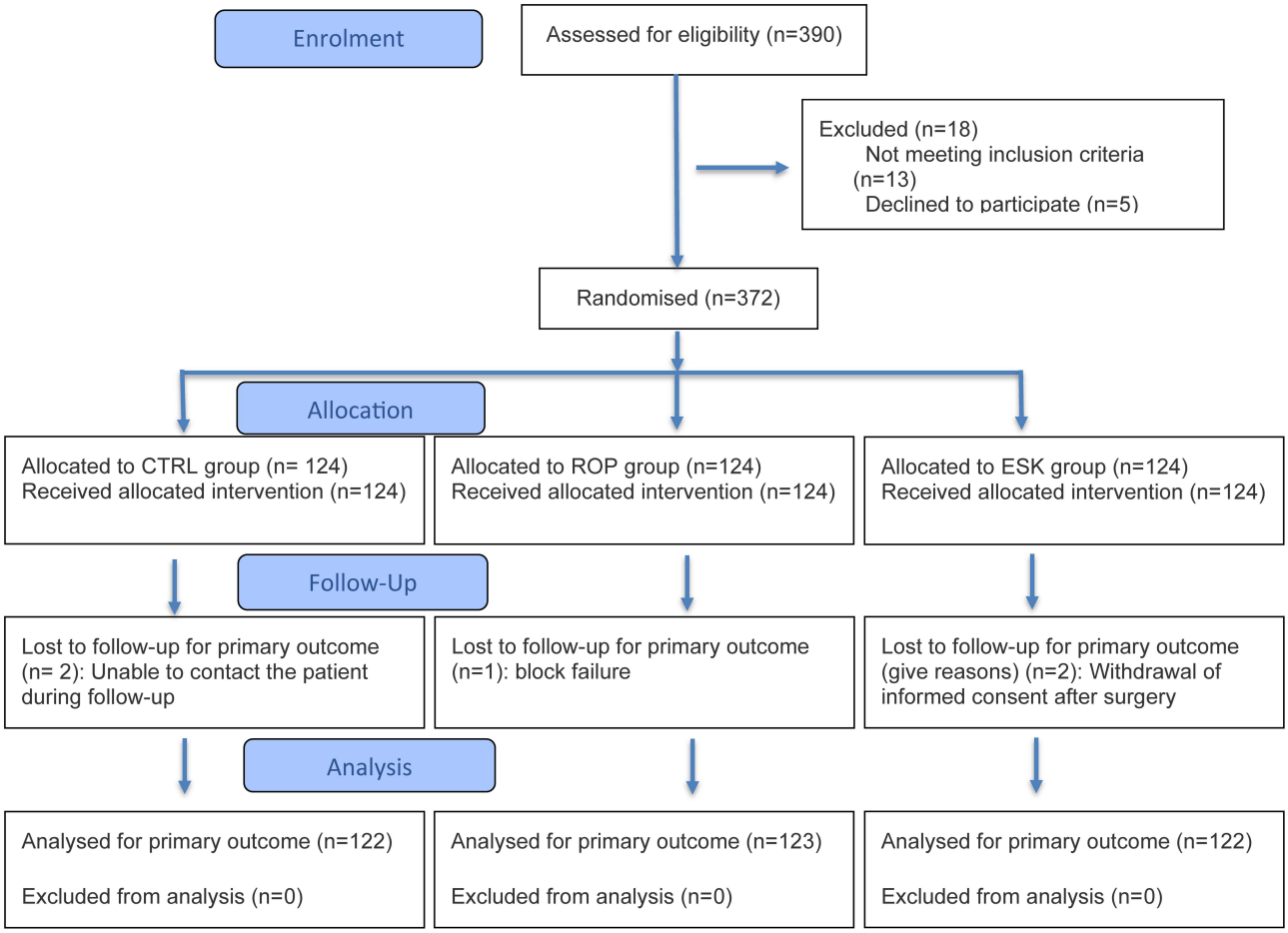

Figure 1 CONSORT flow diagram illustrating patient enrollment, randomization, allocation, follow-up, and analysis in the study of total knee arthroplasty (TKA).

Long-Term Pain Outcomes

The incidence of chronic postsurgical pain (CPSP) showed significant differences among the three groups (Table 2). At 3 months postoperatively, CPSP occurred in 32 patients (32.8%) in the CTRL group, 41 patients (33.3%) in the ROP group, and 20 patients (15.6%) in the ESK group. The incidence did not differ between the CTRL and ROP groups ($P = 0.928$), whereas the ESK group

Table 1 Baseline Characteristics of the Study Participants

Variable	CTRL Group (n=122)	ROP Group (n=123)	ESK Group (n=122)	OR (95% CI)	*P* value
Age (years)	67.3 (9.3)	65.4 (13.5)	67.1 (10.3)	1.01 (0.97–1.05)	0.566
Weight (kg)	64.8(10.3)	63.0 (9.4)	65.8 (10.3)	1.04 (0.79–1.37)	0.800
Height (cm)	158.5 (7.7)	158.5 (8.0)	159.0 (7.7)	0.96 (0.61–1.50)	0.748
Body mass index (kg/m2)	25.7 (3.1)	25.1 (3.4)	26.0 (3.5)	0.90 (0.54–1.49)	0.797
Gender (male/female)	37/85	40/83	35/87	1.02 (0.44–2.37)	0.967
ASA PS	I: 15	I: 9	I: 11	0.90 (0.19–3.98)	0.893
	II: 65	II: 74	II: 79		
	III: 42	III: 40	III: 32		
Duration of surgery (min)	78.5 (22.4)	78.1 (23.7)	73.1(22.1)	1.00 (0.99–1.01)	0.465
Operative side, left/right	63/59	53/70	66/56	1.37 (0.61–3.09)	0.462

Notes: All data are expressed as means (SD) or as absolute numbers.
Abbreviations: ASA PS, American Society of Anesthesiologists Physical Status; OR, Odds Ratio.

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Table 2 Postoperative Analgesic After Total Knee Arthroplasty (TKA)

Outcome	CTRL Group (n=122)	ROP Group (n=123)	ESK Group (n=122)	*P* value
CPSP at 3 months, n (%)	40(32.8%)	41(33.3%)	20(15.6%)	0.928 CTRL vs ROP 0.004 CTRL vs ESK 0.003 ROP vs ESK
CPSP at 6 months, n (%)	32(27.0%)	22(17.9%)	6(4.9%)	0.115 CTRL vs ROP <0.001 CTRL vs ESK 0.001 ROP vs ESK
Morphine consumption (mg)	34.8(11.9)	29.65(11.8)	26.8(11.5)	0.002 CTRL vs ROP <0.001 CTRL vs ESK 0.134 ROP vs ESK
NRS at rest	4.03(1.35)	3.71(1.26)	3.42(1.18)	0.123 CTRL vs ROP <0.001 CTRL vs ESK 0.174 ROP vs ESK
NRS during physiotherapy	4.08(0.75)	3.80(0.68)	3.46(0.66)	<0.001 CTRL vs ROP <0.001 CTRL vs ESK <0.001 ROP vs ESK

Abbreviations: CPSP, chronic postsurgical pain; NRS, Numerical Rating Scale.

demonstrated a significantly lower CPSP rate compared with both the CTRL ($P = 0.004$) and ROP ($P = 0.003$) groups. At 6 months, the incidence of CPSP decreased to 27.0% (32/122) in the CTRL group, 17.9% (22/123) in the ROP group, and 4.9% (6/122) in the ESK group. Although the difference between the CTRL and ROP groups did not reach statistical significance (P = 0.115), the ESK group exhibited a markedly lower CPSP incidence compared with both CTRL ($P < 0.001$) and ROP ($P = 0.001$) groups.

Postoperative pain intensity over time was quantified using the area under the NRS–time curve (AUC) for each group (Figure 2A). The cumulative pain burden, reflected by the AUC, differed significantly among the three groups ($P < 0.0001$). The ESK group (559.3 ± 59.0) showed a markedly smaller AUC than both the ROP group (641.9 ± 55.8) and the CTRL group (679.2 ± 58.5) ($P < 0.0001$ for both comparisons), indicating a more prolonged analgesic effect and a substantially lower overall pain experience during the 6-month follow-up period (Figure 2B).

Opioid Consumption

Cumulative intravenous morphine equivalent consumption within the first 24 hours after surgery differed significantly among groups. Patients in the ESK group required less opioid (26.8 ± 11.5 mg) compared with those in the CTRL group (34.8 ± 11.9 mg, $P < 0.001$) and the ROP group (29.7 ± 11.8 mg, $P = 0.134$). The CTRL group also showed significantly higher opioid consumption than the ROP group ($P = 0.002$). These results indicate that the addition of esketamine to ropivacaine further reduced postoperative opioid requirements within the first 24 hours. (Table 2).

Acute Pain Scores

Postoperative pain intensity at 24 hours differed significantly among groups (Table 2). At rest, NRS scores were lower in the ESK group (3.42 ± 1.18) than in the CTRL group (4.03 ± 1.35, $P < 0.001$), with no significant difference versus ROP (3.71 ± 1.26, $P = 0.174$). During physiotherapy, both ESK (3.46 ± 0.66) and ROP (3.80 ± 0.68) groups reported lower pain scores than CTRL (4.08 ± 0.75, both $P < 0.001$), and ESK provided greater analgesia than ROP ($P < 0.001$).

Functional Recovery

Functional recovery at 24 hours postoperatively differed significantly among groups (Table 3). Patients in the ESK group demonstrated faster early mobilization, with shorter TUG test durations (24.5 ± 4.6 s) compared with the ROP (26.3 ± 4.3 s, $P = 0.004$) and CTRL (30.5 ± 3.5 s, both $P < 0.001$) groups. Walking distance within 24 hours was also greater in the ESK group (21.9 ± 8.5 m) than in the ROP (19.9 ± 7.9 m, $P = 0.122$) and CTRL (14.0 ± 7.4 m, $P < 0.001$) groups.

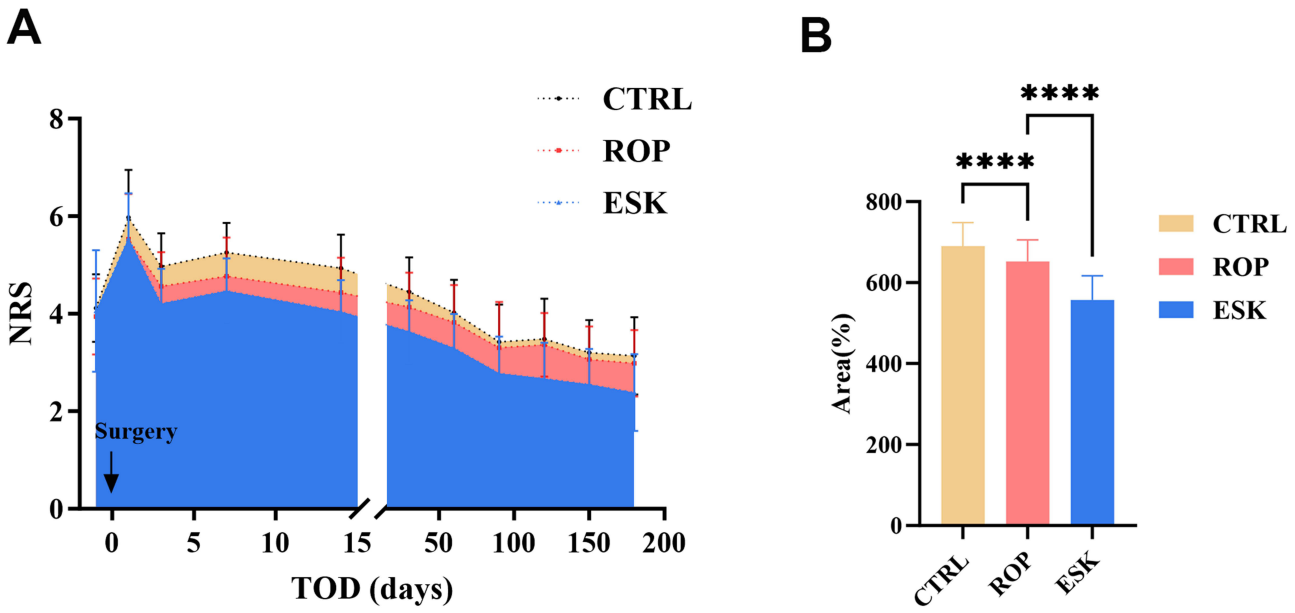

Figure 2 Postoperative pain trajectories and cumulative pain intensity after total knee arthroplasty (TKA). (**A**) Time course of Numeric Rating Scale (NRS) pain scores in the control (CTRL), ropivacaine (ROP), and esketamine (ESK) groups. Pain intensity was assessed from the day before surgery through 6 months postoperatively. Data are presented as mean ± SEM. (**B**) Comparison of the area under the NRS–time curve (AUC) among groups. TOD, Time after Operation Day. ****P<0.0001.

Similarly, QoR-15 scores at 24 hours were highest in the ESK group (129.8 ± 10.6) compared with ROP (124.8 ± 11.3, $P = 0.004$) and CTRL (120.8 ± 13.9, both $P < 0.001$) groups, indicating better perceived recovery quality.

Adverse Events

The incidence of postoperative adverse events, including dizziness, nausea/vomiting, hypotension, hypertension, urinary retention, hyperglycemia, and signs of local anesthetic systemic toxicity, did not differ significantly among the three groups (all $P > 0.05$). No serious adverse events or psychomimetic effects attributable to esketamine were reported (Table 4).

Table 3 Postoperative Recovery Profiles

Outcome	CTRL Group (n=122)	ROP Group (n=123)	ESK Group (n=122)	*P* value
QoR-15 preoperative	129.6 (12.2)	129.9 (10.7)	130.5 (11.7)	0.958 CTRL vs ROPI 0.784 CTRL vs ESK 0.920 ROPI vs ESK
QoR-15 24h	120.8 (14.0)	124.8 (11.3)	129.8 (10.6)	<0.001 CTRL vs ROPI <0.001 CTRL vs ESK 0.004 ROPI vs ESK
TUG test	10.2 (1.9)	10.3 (2.0)	10.3 (2.0)	0.892 CTRL vs ROPI 0.758 CTRL vs ESK 0.965 ROPI vs ESK
TUG test at 24h	30.5 (3.5)	26.3 (4.3)	24.5 (4.6)	<0.001 CTRL vs ROPI <0.001 CTRL vs ESK 0.004 ROPI vs ESK
Distance walked at 24h	14.0 (7.4)	19.9 (7.9)	21.9 (8.5)	<0.001 CTRL vs ROPI <0.001 CTRL vs ESK 0.122 ROPI vs ESK

Abbreviations: Qor-15, quality of recovery-15 questionnaire; TUG test, timed up and go test.

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Table 4 Perioperative Complications

Adverse Event	CTRL Group (n=122)	ROP Group (n=123)	ESK Group (n=122)	*P* value
Dizziness	7 (5.7)	8 (6.5)	15 (12.3)	0.124
Nausea/vomiting	18 (14.8)	12 (9.8)	14 (11.5)	0.473
Hypotension*	3 (2.5)	5 (4.1)	7 (5.7)	0.433
Hypertension†	3 (2.5)	6 (4.9)	4 (3.3)	0.581
Urinary retention	6 (4.9)	4 (3.3)	6 (4.9)	0.762
Local anesthetic systemic toxicity	0 (0)	0 (0)	0 (0)	/

Notes: Values are expressed as n (%). *Hypotension was defined as a ≥25% decrease in systolic blood pressure from baseline or systolic pressure <90 mmHg; †hypertension was defined as a ≥25% increase in systolic blood pressure from baseline or systolic pressure >160 mmHg.

Discussion

In this randomized, double-blind trial, we demonstrated that the perineural administration of esketamine as an adjuvant to ropivacaine for genicular nerve block (GNB) and IPACK block significantly reduced the incidence of CPSP at both 3 and 6 months after total knee arthroplasty (TKA), compared with ropivacaine alone or no block. The ESK group also showed lower postoperative opioid consumption, better pain trajectories over time, faster functional recovery, and no increase in notable adverse events. To our knowledge, although esketamine has been investigated involving TKA, our study is the first randomized clinical trial to evaluate perineural administration of esketamine as an adjunct to peripheral articular nerve blocks (GNB and IPACK) for TKA. We demonstrated that this approach significantly reduces chronic postsurgical pain, suggesting a potential role for perineural esketamine in long-term pain prevention.

Mechanistically, esketamine alleviates pain primarily through N-methyl-D-aspartate (NMDA) receptor antagonism, thereby dampening excitatory neurotransmission and neuronal hyperexcitability within both spinal and supraspinal circuits[19]. Ketamine blocks NMDA receptors by reducing the mean open time of the ion channel and decreasing channel-opening frequency through an allosteric mechanism.[20] Beyond its central actions, esketamine also exhibits peripheral analgesic and anti-inflammatory properties. It stabilizes nociceptor membranes through modulation of voltage-gated sodium and calcium channels and inhibits leukocyte activation, leading to reduced release of interleukins and tumor necrosis factor-α in patients undergoing modified radical mastectomy.[21] Similarly, (R)-ketamine pretreatment ameliorates LPS-induced cytokine elevation and splenomegaly in mice.[22] Given that inflammation contributes to pain sensitization, the ability of ketamine to attenuate C-reactive protein and IL-6 levels further supports its antihyperalgesic and immunomodulatory roles.[23] Consistent with these mechanisms, our findings suggest that esketamine as an adjuvant to regional anesthesia, provides sustained postoperative analgesia, facilitates early functional recovery, and ultimately reduce the risk of chronic postsurgical pain.

Previous studies have mainly focused on the role of peripheral nerve blocks in acute pain control and opioid-sparing effects, while their impact on preventing chronic postsurgical pain (CPSP) remains controversial.[24] Retrospective analyses have reported modest reductions in long-term opioid use with peripheral nerve blocks,[9] but not consistent decreases in chronic pain incidence.[25] In our study, peripheral nerve blocks significantly reduced the incidence and intensity of acute postoperative pain compared with the control group. Although statistical differences were detected in pairwise comparisons at 3 months, a clearer and clinically more meaningful reduction in CPSP incidence was observed at 6 months. These findings suggest that the perioperative use of peripheral nerve blocks may still play a beneficial role in mitigating long-term pain chronification after surgery.

Similarly, esketamine (or ketamine) has been studied mainly in systemic or epidural use for reducing persistent pain, with mixed results.[26,27] Few studies have explored its co-administration at the perineural level. Based on its pharmacologic properties and the technique used in our trial, we hypothesized that both peripheral and central mechanisms may contribute to its analgesic effects. Peripherally, esketamine may enhance sensory nerve blockade and reduce neuroinflammatory signaling, while limited systemic absorption may still provide mild central NMDA receptor antagonism. Our

data support the concept that local use of esketamine may provide a "double hit" — reinforcing peripheral blockade and modulating central sensitization — a design less vulnerable to systemic side effects.

This study has several limitations and potential sources of bias. First, it was a single-center trial, which may introduce selection bias and limit the generalizability of the findings. Second, although all nerve blocks were performed by experienced anesthesiologists, slight technical variations are unavoidable and could have introduced performance bias. Third, the follow-up period was limited to six months, and potential long-term analgesic effects beyond this timeframe remain unknown.Finally, psychological and psychosocial factors known to influence chronic pain development were not assessed, which may contribute to residual confounding.

Our findings suggest that esketamine as an adjuvant to local anesthetic blocks may become a valuable strategy in optimizing perioperative analgesia protocols, particularly for surgeries with high CPSP risk like TKA. Given its favorable safety profile in our study, this approach could be integrated into multimodal analgesia pathways to help prevent chronic pain development. Future research should aim to: Incorporate mechanistic endpoints, such as quantitative sensory testing, functional imaging, or neurophysiological measures, to elucidate central vs peripheral contributions.

Conclusion

In patients undergoing TKA, the addition of esketamine to ropivacaine in genicular and IPACK blocks significantly reduced the incidence of chronic postsurgical pain at 6 months, improved pain trajectories and functional recovery, and did so without increased adverse events. This strategy offers a promising adjunct to multimodal analgesia in the prevention of chronic postoperative pain. Further multicenter studies with extended follow-up and mechanistic investigations are warranted to confirm these results and optimize dosing strategies.

Data Sharing Statement

The datasets generated and analyzed during the present study are not publicly available due to patient privacy restrictions but are available from the corresponding author Dr. Linmin Pan on reasonable request.

Ethical Approval

The study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China (Approval No. KY2023-097), and conducted in accordance with the Declaration of Helsinki and relevant national regulations. Written informed consent was obtained from all participants prior to study enrollment.

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Disclosure

The author(s) report no conflicts of interest in this work.

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