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CLINICAL TRIAL REPORT

S-Ketamine Reduces the Risk of Rebound Pain in Patients Following Total Knee Arthroplasty: A Randomized Controlled Trial

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Purpose: Investigating the effectiveness of S-ketamine in reducing rebound pain (RP) following total knee arthroplasty.

Patients and Methods: This study was a randomized, double-blind, placebo-controlled trial involving 356 adult patients undergoing total knee arthroplasty. Patient enrollment occurred between April and October 2023, with in-person follow-up assessments conducted from admission to 3 days post-surgery. Participants were randomly assigned to the S-ketamine group (n = 178) and the placebo group (n = 178). In the S-ketamine group, participants received a continuous intraoperative infusion of S-ketamine at a dose of 0.30 mg/(kg·h) from the completion of spinal anesthesia until the beginning of joint cavity closure, whereas the placebo group received a continuous infusion of 0.9% saline at the same volume and duration. The primary outcome was the incidence of RP within 12 hours post-surgery. Secondary outcomes included the incidence of RP within 24 hours, time to RP onset, time to first rescue analgesia, pain scores, opioid consumption, clinical outcomes, and harms.

Results: RP was observed in 21.3% of patients in the S-ketamine group compared with 34.8% in the placebo group within 12 hours post-surgery (adjusted RR, 0.62; 95% CI, 0.44 to 0.88; $P = 0.008$). The onset of RP was significantly delayed in the S-ketamine group compared with the placebo group (unadjusted HR, 0.60; 95% CI, 0.41 to 0.88; $P = 0.009$). The numerical rating scale during activity and physical therapy was lower in the S-ketamine group than in the placebo group (day 1 AM: unadjusted difference, −1; 95% CI, −1 to 0; $P = 0.011$; day 1 PM: unadjusted difference, −1; 95% CI, −1 to 0; $P = 0.003$; day 1 physical therapy: unadjusted difference, −2; 95% CI, −2 to −1; $P < 0.001$). The quality of recovery score was higher in the S-ketamine group than in the placebo group (unadjusted difference, 5; 95% CI, 5 to 5; $P < 0.001$). Patient satisfaction was higher in the S-ketamine group than in the placebo group (unadjusted difference, 1; 95% CI, 1 to 1; $P < 0.001$).

Conclusions: S-ketamine effectively reduces the risk of rebound pain and delays its onset in total knee arthroplasty. Additionally, S-ketamine can reduce early pain levels, enhance recovery quality, and improve patient satisfaction.

Keywords: S-ketamine, rebound pain, total knee arthroplasty, nerve block

Introduction

Rebound pain (RP) is characterized by a sharp increase in pain intensity following the resolution of peripheral nerve block or neuraxial anesthesia, with an incidence of 49.6%.[1] This phenomenon typically presents as a burning or dull sensation, primarily within the first 24 hours post regional block and lasting for an average of 2 hours.[2] Barry et al[2] introduced a standardized method for measuring RP, defining it as a transition from well-controlled pain (numerical rating scale [NRS] ≤ 3) to severe pain (NRS ≥ 7) within 24 hours of regional block resolution. Although the etiology of

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RP remains incompletely understood, potential contributing factors may include sudden exposure to nociceptive stimuli, elevated preoperative pain intensity, inadequate postoperative analgesia management, hyperalgesia, nerve injury, and inflammation.[3–5] RP has been associated with negative consequences, including impaired recovery quality, increased reliance on opioids, higher rates of emergency room visits, reduced patient satisfaction, and elevated healthcare costs.[3]

Total knee arthroplasty (TKA) remains a major orthopedic procedure that is associated with severe postoperative pain.[6] Perioperative multimodal analgesia is widely regarded as the optimal approach for pain management in TKA,[7,8] with nerve blocks, neuraxial anesthesia, and periarticular drug mixture injections (PMI) serving as key components of these regimens. However, transient acute RP can still occur following the resolution of a nerve block, PMI, or neuraxial anesthesia. Systemic dexamethasone administration has recently been proposed as a potential strategy to mitigate RP.[9] However, the complex mechanisms underlying the development of RP in the postoperative setting underscore the need for further investigation into alternative pharmaceutical interventions. Ketamine, an N-Methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated potential in mitigating central sensitization induced by opioids,[10] peripheral sensitization mediated by NR2B receptors,[11] peripheral inflammatory responses,[12,13] and optimizing postoperative analgesia.[14,15] However, a study by Touil et al[16] found that an anti-hyperalgesic dose of ketamine failed to prevent the development of RP. It is important to note that the findings of this study were limited by insufficient efficacy and potential biases in its design and execution.[17]

S-ketamine, the dextrorotatory isomer of ketamine, exhibits approximately twice the affinity for NMDA receptors compared with the racemic mixture of ketamine. S-ketamine has demonstrated efficacy in mitigating RP following thoracic paravertebral nerve block in thoracic surgery.[18] However, there is a lack of large-scale, prospective, randomized controlled trials assessing the effectiveness of S-ketamine in preventing RP after TKA. Therefore, this study aimed to evaluate the efficacy of S-ketamine in preventing RP after TKA. We hypothesized that S-ketamine would reduce the risk of RP in patients undergoing TKA compared with placebo without causing serious harms.

Materials and Methods

Study Design

This single-center, prospective, randomized, double-blind, placebo-controlled trial was conducted in the Department of Anesthesiology and Joint Surgery at the Affiliated Hospital of Qingdao University. Eligible participants were randomly assigned in a 1:1 ratio to the S-ketamine group (n = 178) or placebo group (n = 178). The trial was reported in accordance with the Consolidated Standards of Reporting Trials guidelines and its extensions. The study protocol and statistical analysis plan were made available online (Supplemental Digital Content 1), and minor adjustments were made to the protocol during the trial (Supplemental Digital Content 2). Ethical approval was obtained from the Medical Ethics Committee of the Affiliated Hospital of Qingdao University on January 20, 2023. The trial was prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2300069044) on March 06, 2023. This study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all eligible and consenting participants before randomization.

Participants

Participants undergoing elective TKA at the Affiliated Hospital of Qingdao University were recruited for this study. Inclusion criteria included adults aged 18 to 75 years, with a body mass index (BMI) between 18.5 and 31.9 kg/m^2, classified as American Society of Anesthesiologists (ASA) physical status I to III, and meeting the established treatment standards for TKA. Exclusion criteria included unsuccessful spinal anesthesia, hemophilic arthritis or Charcot arthropathy, a history of prior ipsilateral knee joint surgery, severe cardio-cerebrovascular conditions (eg, grade III hypertension, significant valvular disease, chronic heart failure, severe arrhythmia, ischemic heart disease, and symptomatic stroke), severe hepatic or renal ailments (eg, Child-Pugh score III or creatinine clearance rate < 35 mL/min), neurological or psychiatric disorders, current or past intracranial hypertension, allergy to local anesthetics, puncture site infections, inability or unwillingness to participate, lack of understanding of written study materials, glaucoma, untreated or poorly managed hyperthyroidism, and obstructive sleep apnea.

Randomization

A clinical trial center staff member, independent of all other aspects of the trial, generated a random allocation sequence in a 1:1 ratio using R 4.2.3. Block randomization with a block length of 4 was employed. The randomization protocols were securely sealed in opaque envelopes, which were sequentially opened by quality controllers at the time of patient enrollment to determine group allocation.

Blinding

Drug administrators prepared the study drugs based on the randomization sequence. Patients, care providers, outcome assessors of benefits and harms, and statistical analysts remained blinded to the randomization scheme. The study was overseen by an independent data and safety monitoring board, which ensured that blinding of patient allocation was maintained until the completion of statistical analysis. In emergencies, the anesthesiologist was authorized to request unblinding of the intervention or adjust the study drug administration. Unblinded patients were included in the intention-to-treat (ITT) analysis set but excluded from the per-protocol (PP) analysis set.

Regional Block Procedures

The regional block procedures utilized in this study included ultrasound-guided distal adductor canal block (ACB), spinal anesthesia, and PMI. ACB was performed under ultrasound guidance using a 0.375% ropivacaine hydrochloride injection (AstraZeneca Pharmaceutical Co., Ltd., Jiangsu, China) at a volume of 20 mL. The anatomical target for ACB was identified within the triangular space defined by the sartorius muscle, vastus medialis muscle, and adductor magnus muscle, encompassing the femoral artery, vein, and saphenous nerve. Successful ACB was confirmed by the absence of cold sensation in the saphenous nerve-innervated region 20 minutes post-nerve block.

Subsequently, spinal anesthesia was performed using a 25 G "Sprotte" needle at the $L_{3/4}$ or $L_{2/3}$ intervertebral space via either a midline or lateral approach. Following confirmation of unobstructed cerebrospinal fluid flow, 10–15 mg of hyperbaric ropivacaine was administered. Patients were positioned laterally for 3–5 minutes before transitioning to a supine position. The efficacy of spinal anesthesia was assessed by evaluating the extent of sensory loss.

Before prosthesis implantation, the surgical team administered a drug mixture containing 100 mg of ropivacaine, 2 mg of compound betamethasone (Hangzhou MSD Pharmaceutical Co., Ltd, Hangzhou, China), and 0.9% normal saline (total volume: 20 mL) into the posterior capsule, collateral ligament, retinaculum, quadriceps tendon, fat pad, and subcutaneous tissue.

Interventions

In the placebo group, patients received a continuous infusion of 0.9% normal saline at a rate of 0.12 mL/(kg·h), initiated immediately after the completion of spinal anesthesia and discontinued before the initiation of joint cavity closure. In the S-ketamine group, patients were administered an intravenous infusion of S-ketamine hydrochloride (Jiangsu Heng Rui Medicine Co., Ltd., Jiangsu, China) prepared using a standard dilution protocol (50 mg S-ketamine with 0.9% normal saline to a total volume of 20 mL, achieving a concentration of 2.5 mg/mL). The infusion was delivered at a constant rate of 0.12 mL/(kg·h), equivalent to 0.30 mg/(kg·h), and was synchronized with the administration schedule of the placebo group. The total dose of S-ketamine did not exceed 0.5 mg/kg. Additionally, all patients received 2 mg of midazolam before the surgical procedure.

Standard Analgesia Procedures

Patients were prescribed 200 mg of celecoxib capsules (Celebrex Pfizer Pharmaceuticals Co., Ltd., Shanghai, China) one day before the scheduled surgery. Postoperatively, a patient-controlled intravenous analgesia device (PCIA) was initiated in the post-anesthesia care unit (PACU). The PCIA device contained sufentanil citrate injection (100 μg, Yichang Renfu Pharmaceutical Co., Ltd., Hubei, China), ondansetron hydrochloride injection (8 mg, Qilu

Pharmaceutical Co., Ltd., Shandong, China), butorphanol tartrate injection (5 mg, Jiangsu Heng Rui Medicine Co., Ltd., Jiangsu, China), and normal saline to a total volume of 100 mL. The PCIA was programmed with a background infusion rate of 1 mL/h, a bolus dose of 2 mL, a lock interval of 15 minutes, and a maximum infusion rate of 10 mL/h, with a total usage time of48 hours.

In the PACU, rescue analgesia with fentanyl citrate injection (50 μg, Jiangsu Nhwa Pharmaceutical Co., Ltd., Jiangsu, China) was administered to patients if their NRS score was ≥ 4 or upon their request for analgesics. Subsequent doses were halved from the initial dose and administered at intervals of no less than 20 minutes. Rescue analgesia was considered effective when the NRS score was reduced to < 4.

In the surgical ward, patients were scheduled to receive the first dose of acetaminophen-oxycodone tablets (5 mg, Fujian Minglong Pharmaceutical Co., Ltd., Fujian, China) two hours postoperatively, with subsequent doses administered every eight hours, for a total of three doses within 24 hours. For patients with a NRS score ≥ 4, meperidine hydrochloride injections (50 mg, Qinghai Pharmaceutical Factory Co., Ltd., Qinghai, China) were administered intramuscularly and could be repeated every 4–6 hours as needed, up to a maximum daily dose of 300 mg. For patients experiencing nausea and vomiting, 0.1 mg/kg ondansetron was administered as an antiemetic.

Outcome Measures

The primary outcome was the incidence of RP within the first 12 hours post-surgery. RP was defined as a transition from well-controlled pain levels (NRS ≤ 3) to severe pain (NRS ≥ 7) in patients undergoing TKA under spinal anesthesia. RP was assessed accurately by using a pain diary (Supplemental Digital Content 3). Researchers provided structured training to patients, caregivers, and nursing staff to ensure the accurate use of pain diary.

Secondary outcomes were evaluated by standardized, trained outcome assessors. The incidence of RP within 24 hours post-surgery was assessed. RP onset time was defined as the interval from the patient's arrival in PACU to the first occurrence of a NRS ≥ 7. Time to first rescue analgesia was defined as the duration between PACU admission and the first instance of NRS score ≥ 4. The modified rebound pain score (MRPS) was calculated as follows: MRPS = Highest NRS within 24 hours ($HNRS_{24}$) - Lowest NRS in the PACU ($LNRS_{24}$). Pain intensity was evaluated using the NRS at rest, during activity, and physical therapy. NRS at rest referred to pain experienced while stationary. NRS during activity was recorded during the lifting of the affected limb at least 30 cm, repeated five times. NRS during physical therapy corresponded to the highest pain score reported by patients undergoing rehabilitation with a Continuous Passive Motion machine. Assessments were conducted at two intervals, 8:00–10:00 AM and 8:00–10:00 PM, on postoperative days (POD) 1–2 following surgery. Rescue analgesic dosages were evaluated at 12, 24, and 48 hours post-surgery and converted to oral morphine equivalents.[19] The Timed Up and Go test was performed preoperatively and POD 1, measured the time required for a patient to stand from a chair, walk 3 meters, and return to a seated sitting. The active range of motion (AROM) of the knee was assessed preoperatively, while both active and passive range of motion (PROM) were evaluated on POD 1. The time to meet discharge criteria was defined as the point at which a patient could independently ambulate from the bed to the bathroom without walker assistance. Hospital stay was measured as the duration from admission to discharge. The Quality of Recovery (QoR)-15 score was assessed preoperatively and on POD 1. Patient satisfaction at discharge was categorized as "satisfied" (score of 3), "relatively satisfied" (score of 2), and "dissatisfied" (score of 1).

All predefined harms were systematically assessed using a combination of structured and unstructured methods, including questionnaires, clinical examinations, passive patient reporting, and active patient reporting. Harms were monitored from the intervention period through 24 hours post-surgery or until event resolution. Early nausea and vomiting, defined as events occurring intraoperatively and within the first 12 hours postoperatively, were graded for severity using a visual analogue scale (VAS). Tachycardia was defined as a heart rate exceeding 100 beats per minute, while bradycardia was defined as a heart rate below 50 beats per minute. Hypertension was classified as systolic blood pressure exceeding 180 mmHg or increasing by more than 20% from baseline, whereas hypotension was defined as systolic blood pressure below 90 mmHg or a reduction exceeding 20% from baseline. Hypoxemia was defined as an oxygen saturation falling below 93% in the absence of supplemental oxygen. Psychiatric complications associated with S-ketamine included delirium, nightmares, agitation, and hallucinations (auditory, visual, or somatic). Patients were

specifically queried about hallucinations: visual hallucinations were assessed by asking about perceptions of images, individuals, or lights unseen by others; auditory hallucinations were investigated by inquiring about sounds, conversations, or noises imperceptible to others; and somatic hallucinations were evaluated through questions about sensations such as touch, crawling, or bodily perceptions in the absence of external stimuli. Agitation was measured using the Riker Sedation-Agitation Scale (SAS), with SAS scores ≥ 5 indicating agitation. Nightmares were assessed during S-ketamine administration and within the first 24 postoperative hours. Delirium within the initial 24 hours post-surgery was evaluated using the validated Chinese version of the 3D-CAM. Nerve injury, wound infections, deep vein thrombosis, and pulmonary embolism were documented using an electronic medical recording system.

Sample Size

The incidence of severe postoperative pain in patients, undergoing TKA within a multimodal analgesic regimen was reported to range from 25% to 40%.[20,21] Given the variability in multimodal analgesia protocols, a pilot study was conducted involving 20 patients undergoing unilateral TKA. The pilot data revealed an incidence of severe pain (NRS ≥ 7) within the first 12 hours postoperatively of 48%. Therefore, the incidence of RP in patients undergoing TKA and receiving multimodal analgesia was estimated to be 45%, with an anticipated 35% relative reduction in RP incidence within the first 12 hours post-surgery in the S-ketamine group. Sample size calculations were performed using a significance level (α) of 0.05 and a power of 80% (1-β) with the Power Analysis and Sample Size (PASS) 15.0 software. Accounting for a potential dropout rate of 10%, a total of 356 patients (178 per group) were ultimately included in the study.

Statistical Analysis

Data processing was conducted following predefined data management and statistical analysis plans to ensure the reliability and quality of the outcome data. The primary outcome was analyzed using an ITT and PP analysis set. The ITT analysis set included all randomized patients, regardless of their adherence to the assigned intervention. The PP analysis set included patients who had complete baseline data, met all eligibility criteria, completed all outcome assessments, and demonstrated adherence to the study protocol. Data processing and analysis were performed using R 4.3.0 and SPSS 25.0. Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed data were presented as mean and standard deviation (SD), non-normally distributed data as median and interquartile range (IQR), and categorical data as frequency (n) and percentage (%). Demographic information and baseline characteristics were analyzed using two independent sample t-tests, the Mann–Whitney *U*-test, and the chi-square test. The primary outcome analysis was performed using Modified Poisson regression, with or without adjustment for demographic, baseline, and intraoperative variables.

The ITT analysis set was employed to evaluate the secondary outcomes. As the secondary outcomes were exploratory, no adjustments were made for type I errors arising from multiple comparisons. Kaplan-Meier survival curves and Log rank tests were used to analyze the time to first use of rescue analgesia and the onset of RP within 24 hours. Hazard ratio (HR) and 95% confidence interval (CI) were calculated using one-way Cox regression analysis. Repeated-measures data were analyzed using generalized estimating equations. Independent data between the two groups were evaluated using the Mann–Whitney *U*-test, with pseudo-median differences and 95% CI estimated through the Hodges-Lehmann method. Categorical data were evaluated using the chi-square test, continuous correction chi-square test, or Fisher's exact test. Post hoc subgroup analyses were performed for age, sex, ASA class, disease duration, long-term analgesic usage, tourniquet use time, intravenous steroid, and their interactions. Harms were analyzed using the safety analysis set. All statistical tests were two-tailed, with a predetermined significance level of $P < 0.05$.

Results

Participants

The study population was screened between April 15 and October 15, 2023. Of the 450 patients initially screened, 356 individuals meeting the eligibility criteria were randomly assigned to the S-ketamine group (n = 178) and the placebo group (n = 178) (Figure 1). In-person follow-up assessments were conducted from admission to 3 days post-surgery to

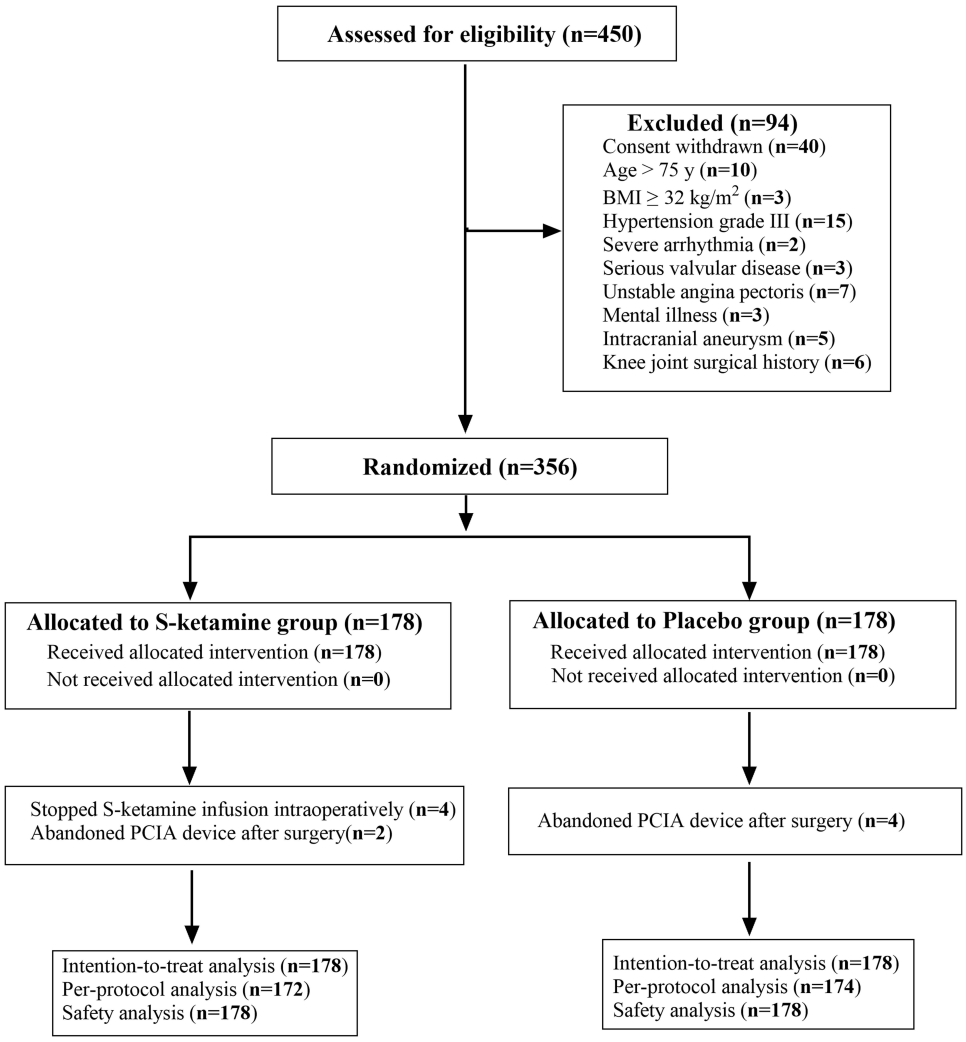

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.
Abbreviation: PCIA, patient-controlled intravenous analgesia.

evaluate both benefits and harms. Throughout the study, the blinding protocol was strictly maintained without any breaches. During the trial, four participants in the S-ketamine group discontinued drug infusion due to transient and severe events, including two patients experiencing severe nausea and vomiting (VAS ≥ 7), one patient exhibiting severe agitation (SAS ≥ 5), and one patient manifesting frequent ventricular arrhythmias. Additionally, two participants in the S-ketamine group and four in the placebo group prematurely discontinued the PCIA device post-surgery due to severe nausea and vomiting. Demographic and baseline characteristics were comparable between the two groups (Table 1).

Primary Outcome

Within the first 12 hours post-surgery, the ITT analysis set indicated that 38 patients (21.3%) in the S-ketamine group experienced RP compared to 62 patients (34.8%) in the placebo group (adjusted RR, 0.62; 95% CI, 0.44 to 0.88; P = 0.008; Table 2). The PP analysis set showed that RP occurred in 37 patients (21.5%) in the S-ketamine group versus 58 patients (33.3%) in the placebo group (adjusted RR, 0.65; 95% CI, 0.45 to 0.93; P = 0.017; Table 2).

Secondary Outcomes

Within 24 hours post-surgery, RP was observed in 44 patients (24.7%) in the S-ketamine group compared to 67 patients (37.6%) in the placebo group (unadjusted RR, 0.66; 95% CI, 0.48 to 0.90; P = 0.010; Table 3). The onset of RP was delayed in the

Table 1 Demographic Information and Baseline Characteristics

Variables	Total (n=356)	Placebo Group (n=178)	S-Ketamine Group (n=178)	*P* value
Age (y)	66 ± 5.0	66 ± 6.0	66 ± 5.0	0.242
Male	88 (24.7%)	46 (25.8%)	42 (23.6%)	0.623
Female	268 (75.3%)	132 (74.2%)	136 (76.4%)	
BMI (kg/m^2)	27 (24.0, 29.0)	27 (25.0, 29.0)	26 (24.0, 29.0)	0.350
ASA				0.519
II	312 (87.6%)	154 (86.5%)	158 (88.8%)	
III	44 (12.4%)	24 (13.5%)	20 (11.2%)	
Duration of illness (y)	10 (5.0, 12.0)	8 (5.0, 12.0)	10 (5.0, 12.0)	0.960
Long-term analgesics use[a]	136 (38.2%)	65 (36.5%)	71 (39.9%)	0.513
CHD	42 (11.8%)	24 (13.5%)	18 (10.1%)	0.324
Hypertension	181 (50.8%)	95 (53.4%)	86 (48.3%)	0.340
Arrhythmia[b]	37 (10.4%)	16 (9.0%)	21 (11.8%)	0.385
Diabetes	43 (12.0%)	25 (14.0%)	18 (10.1%)	0.255
Respiratory disease[c]	57 (16.0%)	27 (15.2%)	30 (16.9%)	0.665
Cerebrovascular disease[d]	21 (6.0%)	13 (7.3%)	8 (4.5%)	0.261
Timed Up and Go test (s)[e]	43 (36.0, 58.0)	43 (35.0, 56.0)	45 (36.0, 60.0)	0.518
AROM (°)[e]	90 (80.0, 90.0)	90 (80.0, 90.0)	90 (80.0, 90.0)	0.105
NRS at rest[e]	0 (0.0, 0.0)	0 (0.0, 0.0)	0 (0.0, 0.0)	0.468
NRS during activity[e]	4 (2.0, 4.0)	4 (2.0, 4.0)	4 (2.0, 4.0)	0.423
Peak NRS in PACU	0 (0.0, 0.0)	0 (0.0, 00)	0 (0.0, 0.0)	0.070
Operation time (min)	75 (65.0, 90.0)	80 (65.0, 88.8)	75 (68.8, 88.8)	0.941
Tourniquet duration (min)	70 (60.0, 80.0)	70 (60.0, 80.0)	70 (60.0, 80.0)	0.440
Intravenous steroid[f]	41 (11.5%)	23 (12.9%)	18 (10.1%)	0.406
Midazolam (mg)	2 (2.0, 2.0)	2 (2.0, 2.0)	2 (2.0, 2.0)	>0.999
Intraoperative analgesia[g]	3 (0.8%)	1 (0.6%)	2 (1.1%)	>0.999
Rescue analgesia in PACU	0 (0%)	0 (0%)	0 (0%)	NE
S-ketamine (mg)	NE	NE	23 (18.8, 27.5)	NE
Infusion volume (L)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.092

Notes: Data is shown as mean ± standard deviation, median (IQR), and number of cases (percentage). [a]Using pain medication daily for at least 7 days in a row within 6 months, taking long-acting pain medication within 3 days, or using any opioid within 24 hours. [b]Arrhythmia includes atrial premature beats, atrial bigeminy, atrial fibrillation, ventricular premature beats, and ventricular bigeminy. [c]Respiratory diseases include asthma and chronic obstructive pulmonary disease. [d]Cerebrovascular disease includes previous ischemic stroke or hemorrhagic stroke. [e]Data was collected the day before surgery. [f]Before the protocol modification, some anesthesiologists administered intravenous steroids, such as dexamethasone and methylprednisolone sodium succinate, to prevent postoperative nausea and vomiting. [g]Rescue pain relief with sufentanil or fentanyl was allowed by the anesthesiologist if spinal anesthesia was not working well enough.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CHD, coronary heart disease; AROM, active range of motion; NRS, numerical rating scale; PACU, post-anesthesia care unit; NE, not estimable.

S-ketamine group compared to the placebo group within the first 24 hours postoperatively (unadjusted HR, 0.60; 95% CI, 0.41 to 0.88, $P = 0.009$; Table 3). Time to first rescue analgesia was longer in the S-ketamine group compared to the placebo group (median survival time; S-ketamine group: 15 hours [14, 16]; placebo group: 10 hours [8, 12]; unadjusted HR, 0.77; 95% CI, 0.59 to 0.99, $P = 0.046$; Table 3). The NRS during activity and physical therapy was lower in the S-ketamine group than in the placebo group on POD 1 (am: unadjusted difference, −1; 95% CI, −1 to 0; $P = 0.011$; pm: unadjusted difference, −1; 95% CI, −1 to 0; $P = 0.003$; physical therapy: unadjusted difference, −2; 95% CI, −2 to −1; $P < 0.001$; Table 3). The QoR-15 score on the POD 1 was higher in the S-ketamine group than in the placebo group (unadjusted difference, 5; 95% CI, 5 to 5; $P < 0.001$). Patient satisfaction at discharge was higher in the S-ketamine group than in the placebo group (unadjusted difference, 1; 95% CI, 1 to 1; $P < 0.001$; Table 3). No significant differences were observed between the groups for other secondary outcomes (Table 3).

Table 2 Primary Outcome

Study Population	Incidence of Rebound Pain Within 12 hours, No./Total (%)		RR (95% CI)	*P* value
	Placebo Group	S-Ketamine Group		
ITT (n=356)[a]				
Model 1[c]	62/178 (34.8%)	38/178 (21.3%)	0.61 (0.43, 0.87)	0.006
Model 2[d]	62/178 (34.8%)	38/178 (21.3%)	0.63 (0.44, 0.89)	0.009
Model 3[e]	62/178 (34.8%)	38/178 (21.3%)	0.62 (0.44, 0.88)	0.008
PP (n=346)[b]				
Model 1[c]	58/174 (33.3%)	37/172 (21.5%)	0.65 (0.45, 0.92)	0.015
Model 2[d]	58/174 (33.3%)	37/172 (21.5%)	0.66 (0.46, 0.94)	0.020
Model 3[e]	58/174 (33.3%)	37/172 (21.5%)	0.65 (0.45, 0.93)	0.017

Notes: The data is displayed as the number of occurrences out of the total, expressed as a percentage. [a]ITT set included all patients who underwent randomization regardless of their intervention. [b]The PP analysis set excludes subjects who did not meet our eligibility criteria or had incomplete adherence to the trial medication. [c]No adjustment for potential confounders. [d]Adjustments were made for gender, age, BMI, ASA class, complications, long-term analgesic use, and baseline pain score. [e]Adjustments were made for gender, age, BMI, ASA class, complications, long-term analgesic use, baseline pain score, operation time, tourniquet use time, utilization of steroids, administration of rescue analgesia during surgery, and midazolam.

Abbreviations: ITT, intention-to-treat; PP, per-protocol; RR, risk ratio; CI, confidence interval.

Table 3 Secondary Outcomes

Variables	Placebo Group (n=178)	S-Ketamine Group (n=178)	RR, Difference or HR (95% CI)[d]	*P* value
Incidence of RP within 24 hours	67 (37.6%)	44 (24.7%)	RR = 0.66 (0.48, 0.90)	0.010
Onset time of RP (h)[a]	NE	NE	HR = 0.60 (0.41, 0.88)	0.009
MRPS (score)	6 (3, 7)	6 (3, 6)	D = 0 (0, 0)	0.329
NRS at resting (score)				
POD 1 AM	2 (2, 4)	2 (2, 4)	D = 0 (−1, 1)	0.279
POD 1 PM	2 (2, 2)	2 (2, 2)	D = 0 (−1, 1)	0.480
POD 2 AM	2 (0, 2)	2 (0, 2)	D = 0 (−1, 1)	0.084
POD 2 PM	2 (0, 2)	2 (0, 2)	D = 0 (−1, 1)	0.082
NRS during activity (score)				
POD 1 AM	4 (4, 6)	3 (3, 6)	D = −1 (−1, 0)	0.011
POD 1 PM	4 (4, 6)	3 (3, 6)	D = −1 (−1, 0)	0.003
POD 2 AM	2 (2, 4)	2 (2, 4)	D = 0 (0, 0)	0.080
POD 2 PM	2 (2, 4)	2 (2, 4)	D = 0 (0, 0)	0.112
NRS during physical therapy (score)				
POD 1	5 (5, 6)	3 (3, 6)	D = −2 (−2, −1)	<0.001
POD 2	3 (3, 6)	3 (3, 6)	D = 0 (0, 0)	0.744
Time to first rescue analgesia (h)	10 (8, 12)	15 (14, 16)	HR = 0.77 (0.59, 0.99)	0.046
Rescue analgesic dosage (mg)[b]				
0–12 hours	0 (0, 11)	0 (0, 11)	D = 0 (0, 0)	0.610
12–24 hours	0 (0, 0)	0 (0, 0)	D = 0 (0, 0)	0.436
24–48 hours	0 (0, 0)	0 (0, 0)	D = 0 (0, 0)	0.095
Timed Up and Go test (s)[c]	8 (−4, 25)	10 (−3, 30)	D = 3 (−2, 7)	0.242
Postoperative AROM (°)	80 (70, 90)	80 (65, 90)	D = 0 (−5, 0)	0.426
Postoperative PROM (°)	96 (87, 110)	95 (80, 110)	D = −2 (−5, 0)	0.163
QoR-15 (score)[c]	−10 (−10, −10)	−5 (−10, −5)	D = 5 (5, 5)	<0.001
Time to discharge criteria (d)	4 (3, 5)	4 (3, 5)	D = 0 (−1, 1)	0.468
Hospital stays (d)	6 (5, 7)	6 (5, 7)	D = 0 (−1, 1)	0.060
Patient satisfaction (score)	2 (2, 3)	3 (3, 3)	D = 1 (1, 1)	<0.001

Notes: The data is displayed in the form of the median (IQR) and number of cases (percentage). [a]Since the incidence of rebound pain was below 50% in both the S-ketamine and placebo groups, the median time could not be calculated. [b]The rescue analgesic dose consists of the bolus dose delivered by the PCIA device and the intramuscular administration of meperidine, necessitating conversion to oral morphine equivalents. [c]Expressed as the absolute difference from the baseline measurement on the first day following surgery. [d]RR, HR, and difference were not adjusted for covariates.

Abbreviations: MRPS, modified rebound pain score; POD, postoperative day; AROM, active range of motion; PROM, passive range of motion; QoR, quality of recovery; NE, not estimable.

Safety Outcomes and Post Hoc Subgroup Analysis

In the S-ketamine group, 11 patients (6.2%) reported hallucinations, whereas no cases were reported in the placebo group (Table 4). The remaining safety outcomes did not show statistically significant differences between the two groups (Table 4). Additionally, post hoc subgroup analysis revealed no significant differences in the risk of RP across the analyzed subgroups (Figure 2).

Discussion

This study found that S-ketamine effectively reduced the risk of RP within the first 12 hours following TKA under spinal anesthesia. Additionally, S-ketamine delayed the onset of RP, extended the time to the first use of rescue analgesics, and lowered pain scores during activity and physical therapy on the first day after surgery. The use of S-ketamine improved postoperative pain management, enhanced the quality of recovery on the initial postoperative day, and increased patient satisfaction at discharge.

The definition of RP is not currently uniform. In this study, we adopted the quantitative criteria proposed by Barry et al,[2] which designate a NRS score of 7 as the threshold for identifying RP. Notably, this definition differs from previous studies by not relying on subjective patient reports of nerve block cessation. Using consistent cutoff values will facilitate data comparison and validation, including incidence rates. Although the VAS is an easy-to-use tool that provides detailed pain levels, its requirement for marking and the need to visualize and mark the line can make it impractical for use in emergencies.[22] On the other hand, the population undergoing TKA is predominantly elderly, and the use of the NRS may offer a practical advantage over the VAS.

Ketamine's pharmacological properties are believed to contribute to its ability to reduce RP; however, evidence of its effectiveness remains inconsistent.[16,23] Limited studies have specifically investigated the efficacy of S-ketamine in preventing RP.[18] Our study indicated that administering S-ketamine effectively reduces the incidence and delays its onset. Notably, the reduction in RP observed in our study lasted up to 24 hours, exceeding the pharmacokinetic half-life of S-ketamine. This extended effect may be attributed to S-ketamine metabolites and non-pharmacological effects.[24,25] Touil et al[16] reported that ketamine did not reduce RP in patients undergoing elective ambulatory upper limb surgery.

Table 4 Harms

Variables	Placebo Group (n=178)	S-Ketamine Group (n=178)	RR (95% CI)	*P* value
Nausea and vomiting	32 (18%)	34 (19%)	1.01 (0.69, 1.64)	0.785
Respiratory depression	2 (1.1%)	2 (1.1%)	1.00 (0.14, 7.02)	>0.999
Hypertension	8 (4.5%)	15 (8.4%)	1.88 (0.82, 4.31)	0.131
Hypotension	2 (1.1%)	3 (1.7%)	1.50 (0.25, 8.87)	>0.999
Tachycardia	3 (1.7%)	4 (2.2%)	1.33 (0.30, 5.87)	>0.999
Bradycardia	2 (1.1%)	7 (3.9%)	7.00 (0.73, 16.62)	0.177
Delirium[a]	8 (4.5%)	10 (5.6%)	1.25 (0.51, 3.01)	0.629
Nightmare	3 (1.7%)	6 (3.4%)	2.00 (0.51, 7.87)	0.311
Agitation[b]	2 (1.1%)	3 (1.7%)	1.50 (0.25, 8.87)	>0.999
Hallucination[c]	0	11 (6.2%)	NE	0.001
Nerve injury	0	0	NE	NE
Wound infection	0	0	NE	NE
Deep vein thrombosis	2 (1.1%)	1 (0.6%)	0.50 (0.05, 5.47)	>0.999
Pulmonary embolism	0	0	NE	NE

Notes: Data is presented as the number of cases (percentage). [a]Delirium was diagnosed using the Chinese version of the 3D-CAM. The 3D-CAM identifies delirium through a diagnostic algorithm based on the four essential features of delirium: (A) acute changes or fluctuations in mental status; (B) inattention; (C) disorganized thinking; and (D) altered level of consciousness. Diagnosis of delirium requires criteria A and B and either or both criteria C and D. [b]Agitation was diagnosed using the Riker Sedation-Agitation Scale (SAS), with a score of 5 or higher indicating agitation. [c]Hallucinations encompass auditory, visual, and somatic hallucinations.

Abbreviation: NE, not estimable.

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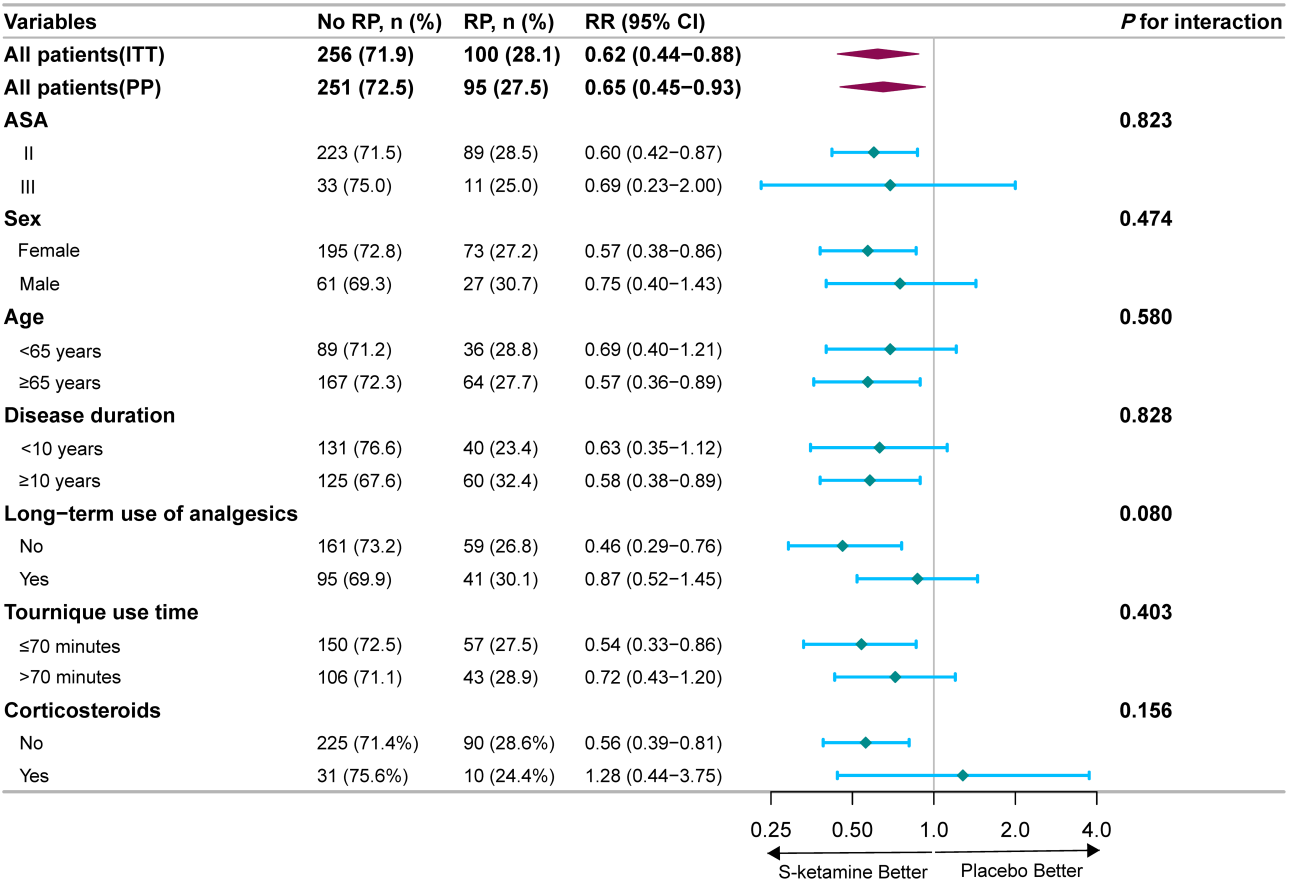

Figure 2 Subgroup analyses and interactions for the primary outcome.
Abbreviations: ITT, intention-to-treat; PP, per-protocol; RP, rebound pain; No RP, no rebound pain.

However, there are two issues concerning the internal validity of this study that warrant further clarification. First, the sample size may have been insufficient to detect a true effect, as 91 patients per group were needed to achieve adequate statistical power, but only 54 were included. Second, randomized controlled trials should be preregistered before patient enrollment to enhance transparency. The delayed registration of this trial may have introduced potential bias in the study's findings. Many studies have reported that adding S-ketamine to the treatment protocol can reduce postoperative opioid consumption and pain scores.[26,27] In contrast, Muñoz-Leyva et al[28] found that, within an established multimodal analgesic regimen, the addition of dexmedetomidine, ketamine, and an extra nerve block did not reduce opioid consumption or pain scores following TKA. Our study demonstrated that intravenous S-ketamine prolonged the time to first rescue analgesia and improved pain scores during activity and physical therapy; however, it did not reduce the total doses of rescue analgesics required. These differences in study findings are likely attributable to variations in multimodal analgesia regimens.

The multimodal analgesia protocol implemented in this study differed from the standard approach recommended by the PROSPECT working group for TKA.[29] This analgesic protocol, developed by a multidisciplinary team of surgeons and anesthesiologists, reflects the routine clinical practice at our center. Given the predominance of elderly patients in the study population, the team accounted for the potential cardiovascular risks associated with conventional NSAIDs or COX-2 inhibitors.[30] Moreover, evidence from previous studies indicates that these agents may have dose- and duration-dependent adverse effects on bone healing.[31,32] RP, characterized by its high intensity, was primarily managed with strong opioids due to their proven efficacy in controlling severe postoperative pain.[33] Additionally, a reduced background opioid dose and the use of prophylactic antiemetics helped to mitigate some of the adverse effects associated with opioid use.

Ketamine as an analgesic adjuvant may provide benefits for early knee mobility and ambulation in patients undergoing TKA,[34] although the available evidence remains inconsistent.[28] Notably, the specific role of S-ketamine in this context has yet to be thoroughly investigated. Effective pain management in TKA is well-documented to lower pain scores, reduce opioid consumption, and improve postoperative rehabilitation and patient satisfaction.[35] Hade et al[36] identified RP as a major factor contributing to patient dissatisfaction among those receiving regional blocks. In our trial, patients receiving S-ketamine demonstrated superior pain management outcomes, improved quality of recovery, and higher patient satisfaction at discharge. These findings highlight the potential of S-ketamine as a valuable adjunct within a multimodal analgesia regimen, offering effective management of postoperative pain and facilitating improved clinical outcomes in TKA procedures.

Neuropsychiatric symptoms, gastrointestinal reactions, and cardiovascular responses were identified as the primary treatment-emergent adverse events associated with ketamine and S-ketamine.[37] The incidence of hallucinations linked to S-ketamine has been reported to range widely, from 1.8% to 15.4%.[38] In our study, hallucinations were observed in 6.2% of patients receiving S-ketamine. This variability may be attributed to differences in drug administration strategies, patient populations, and assessment methodologies. In our study, hallucinations were assessed in a non-systematic manner, with only their presence being recorded and without grading their severity. Notably, follow-up evaluations revealed no significant differences in clinical outcomes between patients who experienced hallucinations and those who did not (Supplemental Digital Content 4). Despite the occurrence of psychiatric side effects, the benefits of S-ketamine in managing acute postoperative pain appear to outweigh its potential harms.[39,40]

This study represents a large-scale trial demonstrating the efficacy of S-ketamine in preventing RP. However, several limitations should be acknowledged: (1) Specific objective measures, such as inflammatory factors, neurotransmitters, and pain thresholds, were not assessed. Consequently, some specific mechanisms by which S-ketamine reduces the risk of RP remain unclear. (2) Currently, standardized tools for identifying RP are lacking. In this study, a checklist integrated into the pain diary was utilized for RP detection. While this tool demonstrated high reliability and validity during internal validation, it has not been externally validated. Further research is necessary to confirm its reliability for precise RP identification. (3) The intervention group received a single dose of S-ketamine, and the optimal dosage for mitigating RP has yet to be established. (4) Opioids were administered via the PCIA device as part of the multimodal analgesic protocol. Therefore, the effectiveness of S-ketamine in reducing RP in a more opioid-restricted context remains uncertain. (5) The assessment of S-ketamine-induced hallucinations and nightmares was conducted in an unsystematic manner, potentially leading to an underestimation of these harms. (6) Although none of the participants required fentanyl for rescue analgesia in the PACU, morphine may be more appropriate given fentanyl's respiratory inhibitory effects.

Conclusions

S-ketamine effectively reduces the risk of rebound pain and delays its onset in total knee arthroplasty. Additionally, S-ketamine reduces early pain levels, enhances recovery, and improves patient satisfaction.

Data Sharing Statement

All source data files are available upon request to the correspondence author.

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Disclosure

The authors declare no competing interests.

References

1. Hamilton DL. Rebound pain: distinct pain phenomenon or nonentity? *Br J Anaesth*. 2021;126(4):761–763. doi:10.1016/j.bja.2020.12.034
2. Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. *Br J Anaesth*. 2021;126(4):862–871. doi:10.1016/j.bja.2020.10.035
3. Nobre LV, Cunha GP, Sousa P, Takeda A, Cunha Ferraro LH. Peripheral nerve block and rebound pain: literature review. *Brazilian J Anesthesiol*. 2019;69(6):587–593. doi:10.1016/j.bjan.2019.05.001
4. Muñoz-Leyva F, Cubillos J, Chin KJ. Managing rebound pain after regional anesthesia. *Korean J Anesthesiol*. 2020;73(5):372–383. doi:10.4097/kja.20436
5. Stone A, Lirk P, Vlassakov K. Rebound pain after peripheral nerve blockade-bad timing or rude awakening? *Anesthesiol Clin*. 2022;40(3):445–454. doi:10.1016/j.anclin.2022.03.002
6. Grosu I, P L, Thienpont E. Pain after knee arthroplasty: an unresolved issue. *Knee Surge Sports Traumatol Arthroscopy*. 2014;22(8):1744–1758. doi:10.1007/s00167-013-2750-2
7. Willinger ML, Heimroth J, Sodhi N, et al. Management of refractory pain after total joint replacement. *Current Pain Headache Rep*. 2021;25(6):42. doi:10.1007/s11916-021-00956-1
8. Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. *J Bone Joint Surg Am*. 2006;88(5):959–963. doi:10.2106/JBJS.E.00344
9. Singh NP, Makkar JK, Chawla JK, Sondekoppam RV, Singh PM. Prophylactic dexamethasone for rebound pain after peripheral nerve block in adult surgical patients: systematic review, meta-analysis, and trial sequential analysis of randomised controlled trials. *Br J Anaesth*. 2024;132(5):1112–1121. doi:10.1016/j.bja.2023.09.022
10. Hayhurst CJ, Farrin E, Hughes CG. The effect of ketamine on delirium and opioid-induced hyperalgesia in the intensive care unit. *Anaesth Crit Care Pain Med*. 2018;37(6):525–527. doi:10.1016/j.accpm.2018.11.001
11. Meng Y, Shen HL. Role of N-methyl-D-aspartate receptor NR2B subunit in inflammatory arthritis-induced chronic pain and peripheral sensitized neuropathic pain: a systematic review. *J Pain Res*. 2022;15:2005–2013. doi:10.2147/JPR.S367982
12. Forget P, Collet V, P L, De Kock M. Does analgesia and condition influence immunity after surgery? Effects of fentanyl, ketamine and clonidine on natural killer activity at different ages. *Eur J Anaesthesiol*. 2010;27(3):233–240. doi:10.1097/EJA.0b013e32832d540e
13. Luggya TS, Roche T, Ssemogerere L, et al. Effect of low-dose ketamine on post-operative serum IL-6 production among elective surgical patients: a randomized clinical trial. *Afr Health Sci*. 2017;17(2):500–507. doi:10.4314/ahs.v17i2.25
14. Riddell JM, Trummel JM, Onakpoya IJ. Low-dose ketamine in painful orthopaedic surgery: a systematic review and meta-analysis. *Br J Anaesth*. 2019;123(3):325–334. doi:10.1016/j.bja.2019.05.043
15. Hannon CP, Fillingham YA, Gililland JM, et al. A systematic review of the efficacy and safety of ketamine in total joint arthroplasty. *J Arthroplasty*. 2023;38(4):763–768.e762. doi:10.1016/j.arth.2022.10.037
16. Touil N, Pavlopoulou A, Barbier O, Libouton X, P L. Evaluation of intraoperative ketamine on the prevention of severe rebound pain upon cessation of peripheral nerve block: a prospective randomised, double-blind, placebo-controlled study. *Br J Anaesth*. 2022;128(4):734–741. doi:10.1016/j.bja.2021.11.043
17. Jen TTH, Victor AD, Jxc K. Role of intraoperative ketamine in preventing severe rebound pain for patients undergoing ambulatory upper extremity surgery. Br J Anaesth. 2022;128. 734–41. doi:10.1016/j.bja.2022.04.021
18. Zeng X, Zhang X, Jiang W, Zhou X. Efficacy of intravenous administration of esketamine in preventing and treating rebound pain after thoracic paravertebral nerve block: a prospective randomized, double-blind, placebo-controlled trial. *Drug Des Devel Ther*. 2024;18:463–473. doi:10.2147/DDDT.S448336
19. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf*. 2016;25(6):733–737. doi:10.1002/pds.3945
20. Grevstad U, Mathiesen O, Lind T, Dahl JB. Effect of adductor canal block on pain in patients with severe pain after total knee arthroplasty: a randomized study with individual patient analysis. *Br J Anaesth*. 2014;112(5):912–919. doi:10.1093/bja/aet441
21. Andersen L, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track Hip and knee arthroplasty. *Anaesthesia*. 2009;64(5):508–513. doi:10.1111/j.1365-2044.2008.05831.x
22. Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: which to use? *Am J Emergency Med*. 2018;36(4):707–714. doi:10.1016/j.ajem.2018.01.008
23. Zhu T, Gao Y, Xu X, Fu S, Lin W, Sun J. Effect of ketamine added to ropivacaine in nerve block for postoperative pain management in patients undergoing anterior cruciate ligament reconstruction: a randomized trial. *Clin Ther* 2020;42(5):882–891. doi:10.1016/j.clinthera.2020.03.004
24. Schwertner A, Zortea M, Torres FV, et al. S-ketamine's effect changes the cortical electrophysiological activity related to semantic affective dimension of pain: a placebo- controlled study in healthy male individuals. *Front Neurosci*. 2019;13:959. doi:10.3389/fnins.2019.00959
25. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet*. 2016;55(9):1059–1077. doi:10.1007/s40262-016-0383-6
26. Bornemann-Cimenti H, Wejbora M, Michaeli K, Edler A, Sandner-Kiesling A. The effects of minimal-dose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial. *Minerva anestesiologica*. 2016;82(10):1069–1076.
27. Brinck ECV, Virtanen T, Mäkelä S, et al. S-ketamine in patient-controlled analgesia reduces opioid consumption in a dose-dependent manner after major lumbar fusion surgery: a randomized, double-blind, placebo-controlled clinical trial. *PLoS One*. 2021;16(6):e0252626. doi:10.1371/journal.pone.0252626
28. Muñoz-Leyva F, Jack JM, Bhatia A, et al. No benefits of adding dexmedetomidine, ketamine, dexamethasone, and nerve blocks to an established multimodal analgesic regimen after total knee arthroplasty. *Anesthesiology*. 2022;137(4):459–470. doi:10.1097/ALN.0000000000004326
29. Lavand'homme PM, Kehlet H, Rawal N, Joshi GP. Pain management after total knee arthroplasty: pROcedure SPEcific Postoperative Pain ManagemenT recommendations. *Eur j Anaesthesiol*. 2022;39(9):743–757. doi:10.1097/EJA.0000000000001691
30. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol*. 2020;17(9):574–584. doi:10.1038/s41569-020-0366-z

31. Dahners LE, Mullis BH. Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft-tissue healing. *J Ame Acad Orthopaedic Surg*. 2004;12(3):139–143. doi:10.5435/00124635-200405000-00001
32. Boursinos LA, Karachalios T, Poultsides L, Malizos KN. Do steroids, conventional non-steroidal anti-inflammatory drugs and selective Cox-2 inhibitors adversely affect fracture healing? *J Musculoskel Neuronal Interactions*. 2009;9(1):44–52.
33. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American pain society, the American society of regional anesthesia and pain medicine, and the American society of anesthesiologists' committee on regional anesthesia, executive committee, and administrative council. *J Pain*. 2016;17(2):131–157. doi:10.1016/j.jpain.2015.12.008
34. Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Anesthesia Analg*. 2005;100(2):475–480. doi:10.1213/01.ANE.0000142117.82241.DC
35. Li JW, Ma YS, Xiao LK. Postoperative Pain management in total knee arthroplasty. *Orthopaedic Surg*. 2019;11(5):755–761. doi:10.1111/os.12535
36. Hade AD, Okano S, Pelecanos A, Chin A. Factors associated with low levels of patient satisfaction following peripheral nerve block. *Anaesthesia Intensive Care*. 2021;49(2):125–132. doi:10.1177/0310057X20972404
37. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*. 2018;5(1):65–78. doi:10.1016/S2215-0366(17)30272-9
38. Lou XJ, Qiu D, Ren ZY, Hashimoto K, Zhang GF, Yang JJ. Efficacy and safety of esketamine for perioperative depression in patients undergoing elective surgery: a meta-analysis of randomized controlled trials. *Asian j Psych*. 2024;95:103997. doi:10.1016/j.ajp.2024.103997
39. Lei Y, Liu H, Xia F, et al. Effects of esketamine on acute and chronic pain after thoracoscopy pulmonary surgery under general anesthesia: a multicenter-prospective, randomized, double-blind, and controlled trial. *Front Med*. 2021;8:693594. doi:10.3389/fmed.2021.693594
40. Chen K, Xie Y, Chi S, Chen D, Ran G, Shen X. Effects of intraoperative low-dose esketamine on postoperative pain after vestibular schwannoma resection: a prospective randomized, double-blind, placebo-controlled study. *Br J Clin Pharmacol*. 2024;90(8):1892–1899. doi:10.1111/bcp.16081