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CLINICAL TRIAL REPORT

The Effect of Intraoperative Infusion of Different Doses of Esketamine on the Quality of Recovery in Elderly Patients Undergoing Knee Arthroplasty

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Objective: This study aimed to investigate the effect of intraoperative intravenous infusion of different doses of esketamine on the quality of postoperative recovery in elderly patients undergoing knee arthroplasty.

Methods: This single-center double-blind controlled trial included 132 elderly patients, who were randomly assigned to four groups. Patients in groups K1, K2, and K3 received an intraoperative intravenous infusion of esketamine (0.1, 0.2, and 0.3 mg/kg) respectively. Patients in the control group (C) received a saline infusion. After surgery, all patients received a patient-controlled intravenous analgesia with sufentanil 2 μg/kg and tropisetron 6 mg, which was activated since pain intensity reached or exceeded 4 on 10. Rescue analgesia was achieved with additional intravenous infusions of 50 mg of flurbiprofen axetil. The primary outcome was the quality of recovery assessed by the QoR-40 score on postoperative day 1 (POD1). Secondary outcomes included the components of the QoR-40, the QoR-40 score on POD2 and 7, pain intensity, rescue analgesic used and the Athens Insomnia Scale (AIS) scores on POD 1, 2 and 7.

Results: The QoR-40 score on POD1 was dose-dependently increased by esketamine, with a significant difference between groups K3 and K2 vs. K1 ($P<0.0001$, $P=0.024$) and C ($P<0.0001$, $P=0.001$), and between groups K3 vs. K2 ($P=0.001$) Only a nonsignificant trend was observed between groups K1 and C. A similar and dose-dependent effect was observed on emotion state and psychological support (improved), and on pain, analgesic consumption and insomnia (reduced), both at POD1 and 2. No longer effect was observed at POD7.

Conclusion: Intraoperative intravenous infusion of esketamine at doses of 0.2 mg/kg/h and 0.3 mg/kg/h improved the quality of recovery on POD1 in elderly patients undergoing knee arthroplasty. The 0.3 mg/kg/h dose of esketamine had the strongest effect, without apparent tolerance issues.

Keywords: esketamine, quality of recovery, arthroplasty, elderly patients

Introduction

With the intensification of population aging in China, the prevalence of osteoarthritis continues to rise, leading to a significant increase in the number of knee arthroplasty surgeries. Over 400,000 total knee arthroplasty (TKA) procedures are conducted annually, with an average annual growth rate of approximately 27.44%.[1] Since the onset of the COVID-19 pandemic (1 March 2020), the number of hip and knee arthroplasties performed worldwide has dropped by approximately 69.14%, yet it has gradually rebounded in recent years.[2,3] The TKA procedures is projected to increase by 401% in 2040 compared with 2014. Owing to population aging, the obesity epidemic and the rising incidence of osteoarthritis, TKA is being increasingly utilized in elderly patients to manage pain and walking impairment caused by knee osteoarthritis.[4] After TKA, 75% of patients reported experiencing pain.[5,6] Elderly patients are inherently prone to

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poor psychological symptoms, and for those with chronic diseases, pain is more likely to have a significant impact on recovery after TKA.[7]

Opioids are essential medications for perioperative analgesia.[8] However, excessive use of opioids may trigger opioid-related adverse effects, such as respiratory depression, nausea, vomiting, gastrointestinal paralysis, sleep disturbances, and hyperalgesia. These complications can also impair the quality of postoperative recovery to varying degrees.[9–11] A systematic review and network meta-analysis have demonstrated that drugs such as lidocaine, dexamethasone, dexmedetomidine and ketamine can all be used to prevent hyperalgesia and improve analgesic efficacy,[12–15] and improve the quality of recovery.

Ketamine, as a potent analgesic and sedative, has clinical practical value. Intravenous injection can reduce the total postoperative opioid consumption and visual analog scale (VAS) scores, relieving pain from orthopedic surgeries.[16] Esketamine is a highly active isomer of ketamine. It exhibits a greater affinity for the N-methyl-D-aspartate receptor (NMDAR) compared to ketamine, resulting in more potent analgesia. Its anesthetic potency is three to four times that of racemic ketamine.[17] Esketamine has a high clearance rate and rapid metabolism in the human body, which enhances the controllability of anesthesia.[18] A meta-analysis showed that perioperative administration of esketamine can improve the early postoperative quality of life in patients.[19]

Intraoperative infusion of esketamine can enhance the quality of recovery in patients undergoing thoracic surgery, bariatric surgery, and breast surgery.[20–22] Some studies have also explored its role in induction of anesthesia and postoperative analgesia for elderly patients receiving joint replacement.[23,24] However, research on the effects of intraoperative intravenous esketamine infusion during knee arthroplasty in the elderly patients remains insufficient.

The QoR-40 assesses five components of patient recovery: physical comfort, physical independence, emotional state, psychological support, and pain. Its scores range from 40 to 200. The QoR-40 demonstrates good validity, reliability, and feasibility.[25]

Therefore, we hypothesized that the esketamine infusion provides the better quality of recovery in patients undergoing knee arthroplasty.

Materials and Methods

Study Design

This study was approved by the Clinical Trial Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2024-KL504-01) and registered with the China Clinical Trial Registry (ChiCTR2500099860). This single-center, prospective, double-blind, randomized controlled trial was conducted from July to September 2025 with written informed consent signed by all participants, and all procedures followed the principles of the Declaration of Helsinki and conformed to the harmonized standards of the guidelines for reporting trials. We maintained the principle of randomization and stopped recruitment until target collection was complete.

Paticipants

We enrolled elderly patients who underwent elective knee arthroplasty at the Affiliated Hospital of Xuzhou Medical University. We included patients who underwent elective knee arthroplasty under general anesthesia and received PCIA; aged 65 years or older; with an American Society of Anesthesiologists (ASA) physical status classification of I–III, a body mass index (BMI) between 18–28 kg/m^2; and signed written informed consent. The exclusion criteria included: allergy to any drug used in the study; with glaucoma, increased intracranial pressure, hyperthyroidism, or pheochromocytoma; uncontrolled or poorly controlled hypertension, grade III hypertension (very high risk), severe arrhythmia, severe cardiovascular and cerebrovascular diseases (arteriosclerosis, coronary heart disease, cardiac insufficiency, lung heart disease, pulmonary hypertension); severe hepatic or renal insufficiency (Child-Pugh class C or requiring renal replacement therapy); who used any tricyclic antidepressant, sedative, opioid, monoamine oxidase inhibitor, or sleep-inducing drug within the past month; inability to cooperate with the researchers.

Patients were allocated to the K1, K2, K3, and C groups using a simple randomization method with a computer-generated random number table The randomization sequence was sealed in opaque envelopes and kept by a designated

custodian. After patient enrollment and completion of preoperative assessment, a researcher not involved in patient treatment or evaluation retrieved the corresponding envelope from the custodian and assigned the patient to a group based on the envelope information. Both the patients and the research evaluators (the same researcher conducted preoperative follow-up, while another collected postoperative data) were blinded to group allocation. The esketamine and saline preparations were prepared in identical 20 mL syringes by an anesthesiologist not responsible for patient follow-up. In this trial, esketamine was diluted with normal saline to a total volume of 20 mL. At the beginning of the surgery, the K1, K2, and K3 groups received intravenous infusion of esketamine at rates of 0.1 mg/kg/h, 0.2 mg/kg/h, and 0.3 mg/kg/h, respectively, until 20 minutes before the end of surgery. The group C received an intravenous infusion of an equal volume of normal saline until 20 minutes before the end of surgery.

Anesthesia Procedure

All patients fasted for 6 hours and were dehydrated for 2 hours. After entering the operating room, a peripheral intravenous line was established. Noninvasive blood pressure, ECG, and pulse oxygen saturation were monitored. Radial artery catheterization was performed to monitor invasive arterial blood pressure. Preoxygenation with 100% oxygen was performed for 3–5 minutes before induction. Induction was then carried out by sequential intravenous administration of midazolam 0.03 mg/kg, etomidate 0.3 mg/kg, sufentanil 0.5 μg/kg, rocuronium 0.8 mg/kg, and tropisetron 2 mg. After jaw muscle relaxation, tracheal intubation was performed for mechanical ventilation with the following parameters: respiratory rate, 12–16 breaths per minute, tidal volume, 6–8 mL/kg, and inspiratory to expiratory ratio, 1:1.5. The end-expiratory carbon dioxide partial pressure was maintained at 35–45 mmHg. Under ultrasound guidance, a femoral nerve block combined with a lateral femoral cutaneous nerve block was performed on the operative side using 20 mL of 0.375% ropivacaine in all patients. Anesthesia was maintained with continuous intravenous infusion of propofol at 4–6 mg/kg/h and remifentanil at 0.1–0.3 μg/kg/min, along with inhalation of 1–2% sevoflurane. Additional rocuronium 0.6 mg/kg was administered as required by the surgical procedure. Based on hemodynamic changes, the anesthesiologist administered vasoactive drugs and adjusted the dosage of maintenance agents to keep heart rate and blood pressure fluctuations within 20% of baseline values. If arterial blood pressure (systolic/diastolic) exceeded 120% of the baseline value or 180/110 mmHg, the researchers administered 10 mg of urapidil. If arterial blood pressure fell below 80% of the baseline value or 90/60 mmHg, the researchers increased the rate of intravenous fluid infusion and gave 40 μg of phenylephrine or 3 mg of ephedrine. If the intraoperative heart rate was less than 50 beats per minute (bpm), atropine 0.5 mg was administered intravenously. In addition, during the intraoperative maintenance phase, when intense surgical stimulation (eg, bone manipulation, nerve traction) or gradual wearing off of the baseline analgesic effect occurred, manifested as tachycardia or a sharp increase in blood pressure exceeding 120% of the baseline value, the anesthesiologist could administer a supplementary bolus of sufentanil 5–10 μg. Inhalation of sevoflurane was discontinued 20 minutes before the end of surgery, and the administration of anesthetic agents was stopped upon completion of skin suturing. All patients were equipped with an intravenous patient-controlled analgesia pump for postoperative analgesia. The pump solution contained sufentanil 2 μg/kg and tropisetron 6 mg, diluted with normal saline to a total volume of 100 mL. The pump parameters were set as follows: a loading dose of 2 mL, a background infusion rate of 2 mL/h, a bolus dose of 0.5 mL, and a lockout interval of 15 minutes. Upon completion of surgery, the analgesia pump was connected, and the patient was transferred to the Post-anesthesia Care Unit (PACU). Flumazenil 0.5 mg and sugammadex 2 mg/kg were administered for reversal, and flurbiprofen axetil 50 mg was given for analgesia. The tracheal tube was removed after the patient resumed spontaneous breathing with an ideal tidal volume (greater than 5 mL/kg), opened their eyes upon verbal command, and regained muscle tone. Patients were transferred back to the ward 30 minutes after extubation and when their modified Aldrete score was≥9. If the patient's pain score was≥4, the analgesic pump was pressed for a bolus dose. If this was still ineffective, flurbiprofen axetil 50 mg was administered intravenously, and repeated if necessary. Ondansetron was used for antiemesis according to the patient's actual condition.

Primary and Secondary Endings

The primary outcome was the quality of recovery score on POD1. We assessed this using the QoR-40, which evaluates five dimensions: physical comfort, physical independence, emotional state, psychological support, and pain. The total score ranges from 40, indicating very poor recovery, to 200, representing excellent recovery.

Secondary outcomes included: the QoR-40 scores on POD2 and 7, NRS scores on POD1, 2, and 7 (ranging from 0 to 10, where 0 indicates no pain and 10 indicates the most extreme pain imaginable), and AIS scores on POD1, 2 and 7 (a total score above 6 indicates insomnia). Additional parameters included operative duration, time to extubation, time spent into PACU, intraoperative consumption of remifentanil and sufentanil (conversion to morphine equivalent dose MED: 1μg of sufentanil is equivalent to 1 mg of morphine, and 10μg of remifentanil is equivalent to 1 mg of morphine), hemodynamic parameters at specific time points: T0 (on admission to the operating room), T1 (before induction), T2 (before intubation), T3 (after intubation), T4 (at the start of surgery), T5 (at the end of surgery), T6 (at extubation), intraoperative fluid intake, use of intraoperative vasoactive agents, flurbiprofen axetil consumptionon on POD1, time to first ambulation, length of hospital stay, and the incidence of postoperative adverse reactions (such as nausea, vomiting, agitation, respiratory depression, hemodynamic instability, drowsiness, hallucinations, and delirium).

Sample Size Calculation

Sample size calculation: one-way ANOVA F-tests. According to the referenced literature,[22] the mean QoR-15 scores on postoperative day 1 for patients undergoing modified radical mastectomy were 110.5, 116.2, and 106.2 in the low-dose esketamine, high-dose esketamine, and control groups, respectively, with standard deviations (SDs) of 8.2, 10.5, and 6.8. Assuming an α of 0.05, a β of 0.1, a dropout rate of 10%, and using a two-tailed analysis, 33 patients were required per group. In contrast, based on our preliminary experimental results, the QoR-40 scores for groups K1, K2, K3, and C were 157.4, 160.3, 166.4, and 155.2, respectively, with standard deviations of 10.5, 7.1, 9.2, and 6.4. With the same assumptions of α=0.05, β=0.1, a 10% dropout rate, and a two-tailed analysis, 27 patients were needed per group. The final sample size was determined to be 33 patients per group, resulting in a total of 132 patients.

Statistical Methods

Statistical analyses were performed using SPSS 25.0 (IBM Corp, Armonk, New York, USA). We employed the Kolmogorov–Smirnov test to assess the normality of data distribution and the Levene's test to evaluate the homogeneity of variances. Normally distributed measurement data are presented as mean ± standard deviation ($x \pm s$). For comparisons between groups, one-way analysis of variance (ANOVA) was used. Pairwise comparisons were conducted using the SNK-q test. Non-normally distributed measurement data are expressed as median and interquartile range (IQR). Group comparisons were performed using the Kruskal-Wallis test, followed by the Dunn test with Bonferroni correction for post-hoc pairwise analysis. And repeated measures data were analyzed with the Friedman test.

Categorical data were analyzed using the chi-square test or Fisher's exact test, as appropriate, and are presented as numbers (%).

All statistical analyses were two-sided, and a *P* value of less than 0.05 was considered indicative of statistical significance.

Results

We adopted a per-protocol analysis in this study. Patients with severe adverse reactions during surgery, operative duration over 3 hours, postoperative ICU admission, or the need for a secondary postoperative surgery were identified as having protocol deviations, and we will exclude these patients from statistical analysis.132 patients were enrolled and randomly assigned to the K1, K2, K3, and C groups. One patient in the K2 group was later excluded due to refusal of follow-up. Therefore, a total of 131 patients were ultimately included in the final analysis: 33 patients each in the K1, K3, and C groups, and 32 patients in the K2 group, as shown in Figure 1.

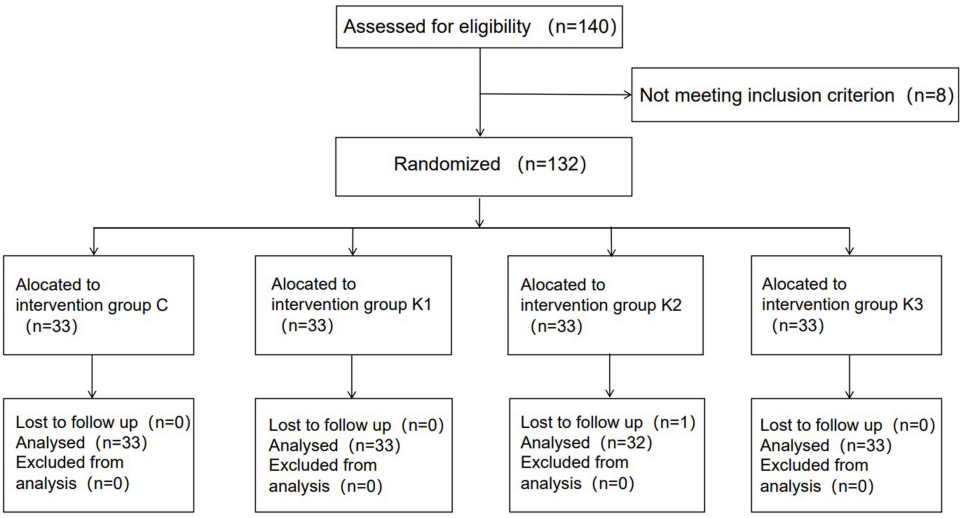

Figure 1 CONSORT flow diagram of the study.

We collected baseline data on patients' general information, including age, gender, BMI, educationanl level, ASA classification, type of knee replacement, medical history, preoperative QoR-40 scores. No significant differences were observed in the baseline data among the four groups of patients, as shown in Table 1.

Primary Outcome Indicator

As shown in Table 2 and Figure 2, the QoR-40 score on POD1 in Group K3 was higher than those in Group C, Group K1 and Group K2 ($P<0.0001$, $P<0.0001$, $P=0.001$ respectively). The QoR-40 score in Group K2 on POD1 was higher than

Table 1 Clinical Data of Patients

Variables	Group C (n = 33)	Group K1 (n = 33)	Group K2 (n = 32)	Group K3 (n = 33)	*P value*
Age, year	68.8±3.3	70.0±3.8	69.5±3.2	69.8±2.9	0.431
Male, n (%)	16 (48.5)	17 (51.5)	15 (46.9)	16 (48.5)	0.995
BMI, kg/m^2	26.4±1.6	26.4±1.7	26.7±1.0	26.5±1.56	0.727
Educational level, n (%)					0.949
Illiteracy	8 (24.2)	9 (27.3)	6 (18.75)	7 (21.2)	
Primary school	13 (39.4)	11 (33.3)	13 (40.625)	9 (27.3)	
Middle school	7 (21.2)	9 (27.3)	7 (21.875)	11 (33.3)	
High school and above	5 (15.2)	4 (12.1)	6 (18.75)	6 (18.2)	
ASA classification, n (%)					0.876
II	25 (75.8)	26 (78.8)	24 (75.0)	23 (69.7)	
III	8 (24.2)	7 (21.2)	8 (25.0)	10 (30.3)	
Type of knee replacement, n (%)					0.902
Total Knee Replacement	26 (78.8)	28 (84.8)	26 (81.3)	28 (84.8)	
Partial Knee Replacement	7 (21.2)	5 (15.2)	6 (18.7)	5 (15.2)	
Medical History, n (%)					
Hypertension, n (%)	18 (54.5)	19 (57.6)	17 (53.1)	19 (57.6)	0.985
Diabetes, n (%)	8 (24.2)	9 (27.3)	8 (25.0)	9 (27.3)	1.000
Stroke history, n (%)	10 (30.3)	10 (30.3)	12 (37.5)	13 (39.4)	0.833
Previous surgery, n (%)	15 (45.5)	15 (45.5)	11 (34.4)	17 (51.5)	0.576
Preoperative QoR-40 Score	160 (155, 165)	160 (155, 163)	158 (155, 163)	159 (155, 164)	0.954

Note: Data are present as the mean ± standard deviation, median (interquartile range), or number.
Abbreviations: Group C, normal saline group; Group K1, an infusion of esketamine of 0.1 mg/kg/h group; Group K2, an infusion of esketamine of 0.2 mg/kg/h group; Group K3, an infusion of esketamine of 0.3 mg/kg/h group; BMI, Body mass index.

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Table 2 QoR-40 Scores Among the Four Groups of Patients

Variables	Group C (n=33)	Group K1 (n=33)	Group K2 (n=32)	Group K3 (n=33)	P^1value
POD1	150 (147, 159)	155 (150, 159)	162 (155, 167)	170 (166, 174)[a]	**<0.0001**
POD2	167 (163, 170)[ab]	170 (167, 172)[ab]	172 (170, 172)[ab]	176 (173, 178)[a]	**<0.0001**
POD7	181 (180, 182)[abc]	181 (180, 182)[abc]	180 (180, 181)[abc]	181 (180, 181)[abc]	0.062
P^2value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	

Notes: Data are present as median (IQR). P^1 is comparison of QoR-40 scores among different groups at the same time point; P^2 is comparison of repeated measurements within the same group; Bold a indicates $P<0.05$ vs. Pre; b indicates $P<0.05$ vs. POD1; c indicates $P<0.05$ vs POD2. Bold values indicate statistically significant values ($P<0.05$).
Abbreviations: Pre, preoperation day; POD, postoperative day.

that in Group K1 and C (P=0.024, P=0.001). The QoR-40 score on POD1 in Group K1 and C was non-significant trends (P=0.149). The QoR-40 score on POD2 was also higher in the K3 group than in the C, K1, and K2 groups (P<0.0001, P<0.0001, P=0.001, respectively). No differences were observed in the QoR-40 scores on POD2 among the K1, K2, and C groups (P=0.166, P=0.058, P=0.230). The QoR-40 scores on POD7 did not differ across the four groups.

We also conducted a repeated-measures analysis of the QoR-40 scores for each group on preoperative day and POD1, 2 and 7. The results showed that the scores in Group K3 on POD1 were already superior to the preoperative scores (P=0.029) in Table 2.

We presented the scores for the five dimensions across the groups in Table 3. Differences between the experimental and control groups were noted in emotional state, psychological support, and pain (P <0.0001, P<0.0001 *and P=0.007, respectively*), whereas no differences were found in physical comfort and self-care ability. Among these, the differences in emotional state among the four groups were largely consistent with the QoR-40 scores on POD1: the K2 and K3 groups scored higher than the K1 and C groups (P=0.004, P=0.003, P<0.001and P<0.0001, respectively), the Group K3 scored higher than the Group K2 (P=0.001). Regarding pain, the Group K1, K2, and K3 performed better than the Group C (P=0.029, P<0.0001 and P<0.0001, respectively). In terms of psychological support, the K2 and K3 groups had lower scores than the K1 and C groups (all P<0.0001).

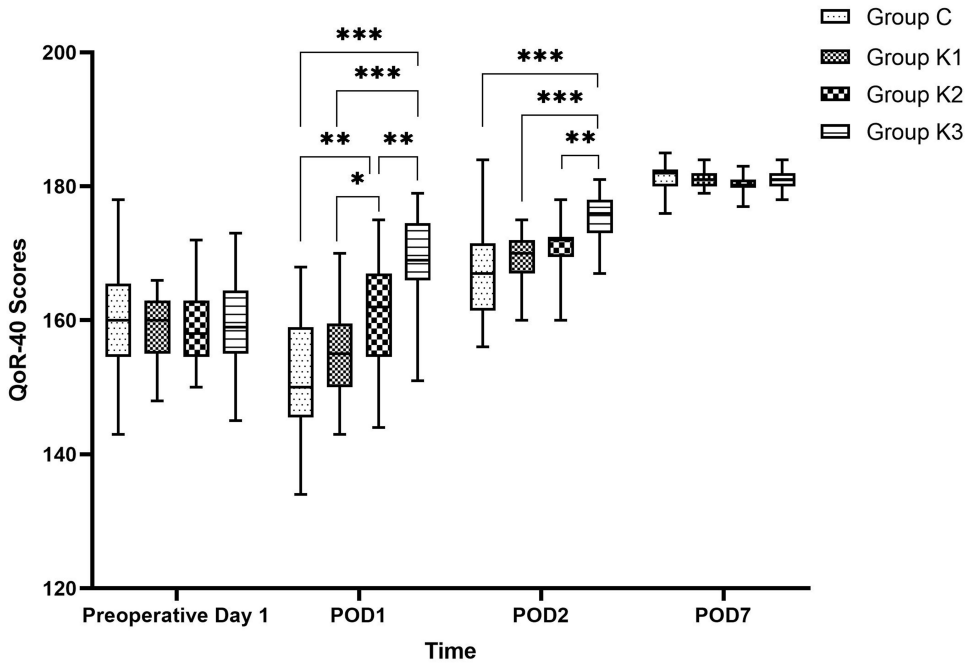

Figure 2 Preoperative and Postoperative Qor-40 Scores of Patients.
Notes: Data are present as median (IQR); *indicates P<0.05 between groups; **indicates P<0.01 between groups; ***indicates P<0.0001 between groups.
Abbreviation: QoR-40, Quality of Recovery 40.

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Table 3 Composition of QoR-40 Scores of Patients on POD1

Variables	Group C (n=33)	Group K1 (n=33)	Group K2 (n=32)	Group K3 (n=33)	*P* value
Physical comfort	50 (46, 52)	50 (48, 52)	50 (47, 51)	50 (49, 52)	0.420
Emotion state	37 (35, 38)	37 (32, 41)	43 (37, 47)[ab]	48 (46, 51)[abc]	**<0.0001**
Physical independence	14 (12.5, 15)	13 (12, 14)	13 (12.5, 14)	14 (13, 14)	0.741
Psychological support	30 (29, 31)	29 (28, 30)	26 (25, 28)[ab]	26 (25, 28.5)[ab]	**<0.0001**
Pain	27 (26.5, 29)	29 (28, 30)[a]	30 (28, 31)[a]	31 (28.5, 32)[ab]	**0.007**

Notes: Data are present as median (IQR). Bold a indicates *P*<0.05 compared with Group C; b indicates *P*<0.05 compared with Group K1; c indicates *P*<0.05 compared with Group K2.

Table 4 The Postoperative NRS and AIS Scores of Patients

Variables	Group C (n=33)	Group K1 (n=33)	Group K2 (n=32)	Group K3 (n=33)	*P* value
NRS1	4 (3, 4)	3 (3, 3)	2 (2, 3)	1 (1, 3)	**<0.0001**
NRS2	3 (3, 4)	2 (2, 3)	2 (1, 2)	2 (1, 2)	**<0.0001**
NRS7	1 (1, 1)	1 (0, 1)	1 (1, 1)	1 (1, 1)	0.278
AIS1	8 (6, 10)	6 (6, 7)	3 (3, 4)	3 (2, 3)	**<0.0001**
AIS2	4 (4, 5)	3 (3, 4)	3 (2, 3)	2 (2, 3)	**<0.0001**
AIS7	2 (2, 4)	2 (2, 3)	2 (2, 2)	2 (2, 2)	**0.015**

Notes: Data are present as median (IQR). Bold values indicate statistically significant values (*P*<0.05).
Abbreviations: NRS1, the Numerical Rating Scale (NRS) scores on POD1; NRS2, the NRS scores on POD2; NRS7, the NRS scores on POD7; AIS1, the Athens Insomnia Scale (AIS) scores on POD1; AIS2, the AIS scores on POD2; AIS7, the AIS scores on POD7.

Secondary Outcome Indicator

There were differences in NRS and AIS scores among the four groups on POD1and 2. As shown in Table 4 and Figure 3A, compared with group C, the NRS scores on POD1 and 2 were lower in groups K1, K2, and K3 (*P*=0.037, *P*<0.0001, *P*<0.001, *P* <0.0001, *P* <0.0001, *P* <0.0001, respectively). The NRS scores on POD1 and 2 in Group K1 were higher than those in Groups K2 and K3 (*P*=0.01, *P*=0.001, *P*=0.024, and *P*=0.029, respectively). No differences was observed between groups K2 and K3 on POD1 and 2 (*P*=0.172, *P*=0.939). There was no difference in NRS scores among the four groups on POD7.

Regarding the AIS scores, as shown in Table 4 and Figure 3B, on POD1 and 2, the AIS scores in Groups K1, K2, and K3 were lower than those in Group C (*P*=0.038, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, respectively). Groups K2 and K3 had lower scores than Group K1 (*P*<0.0001, *P*<0.0001, *P*=0.001, *P*=0.002, respectively), but there was no difference between Groups K2 and K3 (*P*=0.263, *P*=0.894). The AIS scores on POD7 showed differences between the K2, K3 groups and the Group C (*P*=0.046, *P*=0.031, respectively).

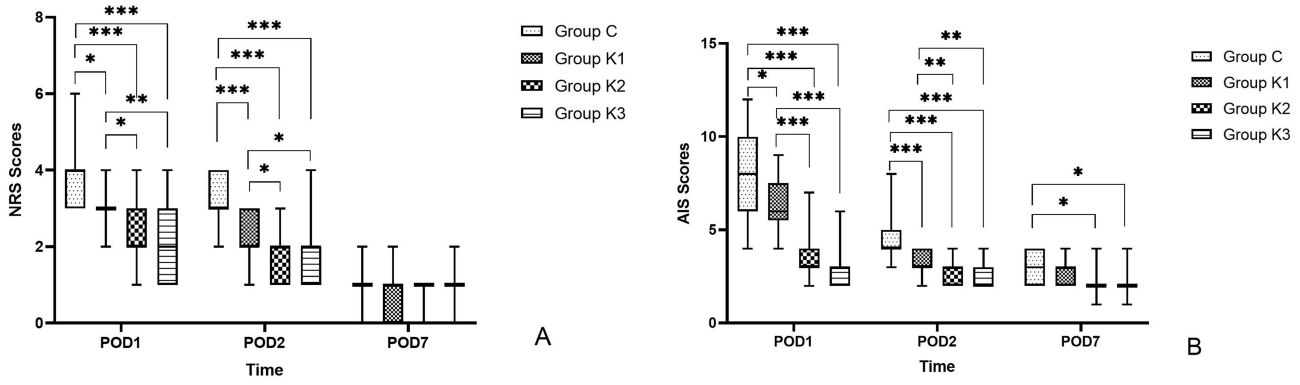

Figure 3 The Postoperative NRS and AIS Scores of Patients. (**A**) The Postoperative NRS Scores. (**B**) The Postoperative AIS Scores.
Notes: Data are present as median (IQR); *indicates *P*<0.05 between groups; **indicates *P*<0.01 between groups; ***indicates *P*<0.0001 between groups.
Abbreviations: NRS, Numerical Rating Scale; AIS, Athens Insomnia Scale.

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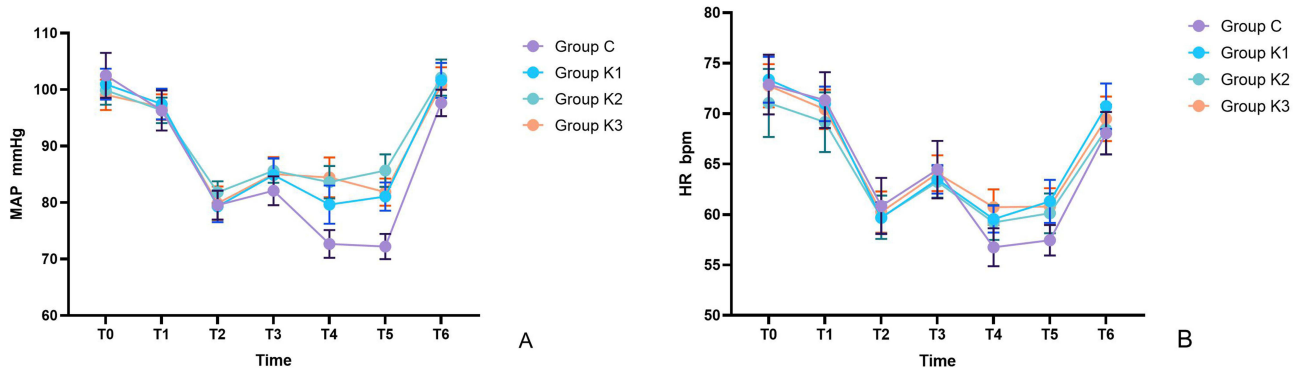

Figure 4 Perioperative MAP and HR. (**A**) Perioperative MAP. (**B**) Perioperative HR.
Note: The 95% CI is used as the margin of error.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; T0, enter the operating room; T1, pre-induction; T2, pre-intubation; T3, post-intubation; T4, the start of surgery; T5, the end of surgery; T6, extubation.

The hemodynamic changes in the four patient groups are shown in Figure 4A and B. As can be observed, there were no significant differences in mean arterial pressure (MAP) and heart rate (HR) among the four groups before the start of surgery. However, the MAP and HR at both the beginning and the end of surgery were higher in groups K1, K2, and K3 compared to group C (P<0.05). No significant difference was found in MAP and HR at extubation time.

In Table 5, there were no differences in surgical duration and intraoperative fluid intake among the four groups. The morphine equivalent dose (MED: 1μg of sufentanil is equivalent to 1 mg of morphine, and 10μg of remifentanil is equivalent to 1 mg) in the K1, K2, and K3 was lower than that in the Group C (P=0.001, P<0.0001, P<0.0001), and there were differences in the dosages of remifentanil and sufentanil among the groups. The sufentanil dosage in Groups K2 and K3 was lower than that in Group C (P=0.024, P=0.002), and the remifentanil dosage in Groups K1, K2 and K3 was lower than that in Group C (P=0.001, P<0.0001, P<0.0001). The intraoperative phenylephrine dosage in the K1, K2, and K3 groups was lower than that in the C group (all $P < 0.0001$), but no statistically differences were observed among the K1, K2, and K3 groups. No statistically differences were found among the four groups in terms of extubation time, time spent into PACU or the use of urapidil. There were no differences in postoperative ambulation time or length of hospital stay among the four groups of patients.

Table 5 The General Conditions of Patients During and After the Operation

Variables	Group C (n=33)	Group K1 (n=33)	Group K2 (n=32)	Group K3 (n=33)	*P* value
Operative duration, min	95 (90, 100)	90 (80, 105)	90 (70, 100)	90 (90, 100)	0.764
MED, mg	155 (150, 160)	130 (120, 150)[a]	125 (120, 145)[a]	120 (110, 130)[a]	**<0.001**
Sufentanil, ug	30 (20, 30)	25 (20, 30)[a]	20 (20, 28.75)[a]	20 (20, 27.50)[ab]	**0.006**
Remifentanil, mg	1.4 (1.25, 1.55)	1.1 (1.0, 1.3)	1.0 (0.9, 1.2)[a]	1.0 (0.9, 1.0)[a]	**<0.0001**
Propofol, mg	260 (250, 290)	250 (250, 282.5)	250 (250, 270)	250 (245, 255)	0.064
Ephedrine, n (%)	8 (24.2)	9 (27.3)	8 (25.0)	5 (15.2)	0.693
Atropine, n (%)	3 (9.1)	1 (3.0)	0 (0.0)	1 (3.0)	0.398
Phenylephrine, n (%)	33 (100)	32 (97.0)	30 (93.8)	32 (93.8)	0.572
Phenylephrine, mg	0.24 (0.20, 0.24)	0.12 (0.08, 0.16)[a]	0.12 (0.08, 0.16)[a]	0.08 (0.08, 0.16)[a]	**<0.0001**
Intraoperative fluid intake, mL	927±187	888±176	850±193	873±132	0.329
Time to extubation, min	10.2±3.1	11.1±3.6	12.5±3.2	13.3±3.8	0.056
Time spent into PACU, min	41.7±5.2	40.2±4.8	42.1±6.0	42.3±4.4	0.359
Urapidilo, n (%)	3 (9.1)	4 (12.1)	3 (9.4)	4 (12.1)	1.000
Time to first ambulation, day	2 (2, 2)	2 (2, 2)	2 (2, 2)	2 (2, 2)	0.328
Length of hospital stay, day	5 (4, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	0.566

Notes: Data are present as median (IQR), mean ± standard deviation or numbers. Bold a indicates P<0.05 compared with Group C; b indicates P<0.05 compared with Group K1. Bold values indicate statistically significant values (P<0.05).
Abbreviations: MED, morphine equivalent dose; PACU, Post-anesthesia Care Unit.

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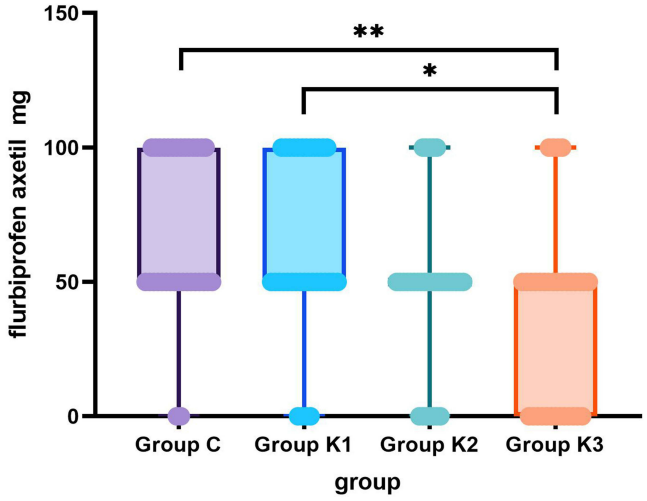

Figure 5 Postoperative flurbiprofen axetil consumption.
Notes: Scatter plot. *indicates $P<0.05$ between groups; **indicates $P<0.01$ between groups.

As is shown in Figure 5, the postoperative flurbiprofen axetil consumption in the K3 group was lower than that in the K1 and C groups ($P=0.014$, $P=0.001$), while no statistically differences were observed between the C and K1 groups or between the K2 and K3 groups ($P=1.000$, $P=1.000$).

The incidence of adverse reactions, including postoperative nausea and vomiting, dizziness, headache, agitation, hallucinations, drowsiness, and delirium, showed no significant differences among the four groups of patients in Table 6 (all $P>0.05$).

Discussion

The knee arthroplasty is frequently selected as the treatment for advanced stage knee disorders in elderly patients. Most patients may experience acute postoperative pain, which can impair sleep and emotional well-being. If poorly managed, this pain may even progress to a chronic condition, significantly compromising the long-term quality of recovery.[26] In this study, we employed the QoR-40 scale to assess the recovery of patients across four groups, evaluating physical comfort, physical independence, emotional state, psychological support, and pain. We found that infusion doses of 0.2 mg/kg/h and 0.3 mg/kg/h improved patients' quality of recovery on POD1 compared with 0.1 mg/kg/h and normal saline. Studies have shown that an increase of 6.3 points in the QoR-40 score indicates improved quality of recovery.[27] Moreover, the score at 0.3 mg/kg/h on POD1 was higher than the preoperative score (159–170). Therefore, esketamine infusion at 0.3 mg/kg/h is also clinically meaningful.

We observed differences between the esketamine groups and the control group in QoR-40 scores on POD1 regarding emotional state, psychological support, and pain. Moreover, the distinctions in scores for emotional state and pain were largely consistent with the overall QoR-40 score pattern on POD1. This may be attributed to the anxiolytic and

Table 6 The Incidence of Adverse Reactions of Patients

Variables	Group C (n=33)	Group K1 (n=33)	Group K2 (n=32)	Group K3 (n=33)	*P* value
Nausea and Vomiting, n (%)	8 (24.24)	8 (24.24)	6 (18.75)	7 (21.21)	0.966
Delirium, n (%)	1 (3.03)	0 (0)	2 (6.25)	0 (0)	0.192
Hallucinations, n (%)	0 (0)	0 (0)	1 (3.13)	0 (0)	0.244
Agitation, n (%)	2 (6.06)	0 (0)	0 (0)	1 (3.03)	0.616
Dizziness, n (%)	4 (12.12)	3 (9.09)	3 (9.38)	3 (9.09)	1.000
Drowsiness, n (%)	3 (9.09)	4 (12.12)	6 (18.75)	6 (18.18)	0.649
Rescue antiemetic, n (%)	6 (18.18)	5 (15.15)	5 (15.63)	5 (15.15)	1.000

Note: Data are present as number (%).

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antidepressant effects of esketamine. Previous studies have found that intravenous infusion of esketamine at doses of 0.20 mg/kg or 0.40 mg/kg can treat depression in adults.[28] This indicates that esketamine may improve the quality of postoperative recovery through its antidepressant effect. Regarding psychological support, the scores of the K2 and K3 groups were lower than those of the K1 and C groups. This may be because, in clinical practice, patients with favorable postoperative recovery generally receive slightly less medical support compared to patients who experience obvious adverse reactions.

Compared with a low dose, high-dose esketamine infusion further improved the quality of recovery on POD1 and 2, while also reducing postoperative NRS and AIS on these two days. This may be attributed to the dose-dependent analgesic effect of esketamine. Compared to low-dose esketamine, high-dose esketamine may prolong the duration of analgesia in patients.[29] Esketamine can inhibit opioid-induced hyperalgesia and damage-induced central sensitization, thereby preventing opioid-induced hyperalgesia and improving postoperative analgesia.[30,31] The discrepancy in remifentanil requirements is more likely due to the analgesic-sparing effect of esketamine. This may also alleviate opioid-induced hyperalgesia by reducing the intraoperative opioid dosage. A systematic review concluded that intravenous ketamine serves as an effective adjunct for postoperative analgesia and is particularly beneficial in abdominal, thoracic, and orthopedic surgeries.[32] Esketamine modulates the emotional component of pain by acting on brain structures such as the cerebral lobes and prefrontal cortex.[33] Furthermore, esketamine can be metabolized in the human body into an active metabolite, esnorketamine, which exhibits a more potent anesthetic effect than esketamine itself. With an elimination half-life of 6 to 10 hours, this metabolite may explain why the analgesic duration of esketamine is prolonged.[34]

Our finding indicated no difference in the QoR-40 scores between the K1 and C groups, and our results showed NRS scores in Group K1 were lower than those in Group C on POD1 and 2. This indicated that infusion of 0.1 mg/kg/h esketamine can improve postoperative analgesia and sleep in patients, but not emotional state. This may be because the 0.1 mg/kg/h dose is lower than the antidepressant effective dose, thus affecting the quality of recovery scores. As previous studies found intravenous infusion of esketamine at doses of 0.20 mg/kg or 0.40 mg/kg can produce obvious antidepressant effects, while the optimal dosing, and the lowest effective dose remains to be established, especially doses<0.20 mg/kg.[28,35] There were no differences in NRS and AIS scores between Groups K2 and K3, which may be related to our administration method and dose selection. Intravenous infusion of low-dose esketamine during modified radical mastectomy did not improve pain scores on POD1.[20] Previous studies have found that in laparoscopic total hysterectomy, the postoperative VAS scores in the high-dose 0.5 mg/kg esketamine group were significantly lower than those in all other groups. However, no significant difference was observed between the low-dose 0.25 mg/kg esketamine group and the 0.5 mg/kg racemic ketamine group.[36] Also, the administration of low-dose intravenous ketamine also did not improve the quality of recovery in patients following laparoscopic cholecystectomy.[37] These findings also suggest that the impact of different doses of esketamine on postoperative recovery may be related to multiple factors, including the type of surgery, patient population, and method of administration.

The AIS scores on POD1 and 2 showed that the esketamine could improve operative sleep quality. And the scores on POD 7 also indicated Group K2 and K3 had better sleep quality than Group C and K1. Regarding the improvement of sleep quality, esketamine may enhance dopamine release in the prefrontal cortex through mechanisms such as anticholinergic effects and NMDA receptor antagonism. This can increase rapid eye movement (REM) sleep latency, reduce REM sleep duration, and thereby improve sleep architecture.[38] Esketamine may also alleviate postoperative pain by activating intraoperative prefrontal electroencephalographic activity and inducing alpha spindle oscillations, thereby improving postoperative sleep quality.[39] The anti-inflammatory effect of esketamine may help prevent postoperative sleep disturbances by regulating circadian rhythms through the modulation of clock genes.[40] Notably, pain and psychological status are also significant contributors to postoperative sleep disturbances. Poor psychological status increases the risk of chronic postoperative pain, whereas both pain and opioid use can disrupt sleep. In turn, sleep disturbances tend to lower the pain threshold.[41,42] Therefore, a significant vicious cycle exists between postoperative pain and postoperative sleep.

Based on our findings, esketamine may enhance the postoperative recovery quality scores in elderly patients by improving pain, emotional state, and sleep disturbances (especially 0.2 and 0.3mg/kg/h infusion). These aspects are not isolated but can mutually influence each other.

Compared with younger patients, elderly patients exhibit a diminished capacity for physiological regulation of the circulatory system, rendering them more susceptible to hypotension or bradycardia during the induction and maintenance phases of general anesthesia. In this study, patients in the esketamine groups exhibited higher mean arterial pressure and heart rate at both the start and end of surgery compared to the control group, along with a reduction in phenylephrine consumption. These findings are consistent with previous conclusions that esketamine helps maintain hemodynamic stability in patients under general anesthesia.[23] Esketamine can exert sympathomimetic effects and stimulate the cardiovascular system in a concentration-dependent manner, thereby reducing the incidence of hypotension and bradycardia.[43,44] Esketamine reduces intraoperative opioid consumption.[21,30] Intraoperative remifentanil consumption was reduced by esketamine, consistent with our findings.

Neither extubation time nor PACU stay time was prolonged in the esketamine groups, and no differences were observed in the incidence of postoperative delirium or agitation. This may be because previous studies typically administered a loading dose of esketamine firstly, followed by continuous pumping until the end of the surgery. In contrast, we only used intraoperative intravenous pumping with a maximum dose of 0.3 mg/kg/h, which was not high, and the pumping was stopped 20 minutes before the end of the surgery. Some patients may experience hallucinations or drowsiness after receiving esketamine, which can generally be suppressed by concomitant administration of appropriate propofol or midazolam.[29] Therefore, in our study, esketamine did not significantly prolong the postoperative extubation time or increase the incidence of postoperative delirium in elderly patients.

This study was a single-center trial. The results showed that the intervention did not shorten the length of hospital stay or mobilization time, nor did it reduce medical costs. Multicenter trials with extended follow-up periods may be conducted in the future to explore its impact on patients' long-term prognosis and overall health. When esketamine is administered intraoperatively as an adjunct, we may appropriately reduce the intraoperative opioid dosage based on the actual conditions. This may provide satisfactory analgesia while further lowering the risk of opioid-related adverse reactions and opioid-induced hyperalgesia.

As noted in our previous discussion of existing research, administering only a loading dose or subsequent intravenous infusion of esketamine during surgery can improve the quality of recovery for patients undergoing procedures in the thoracic surgery, as well as in bariatric and breast surgery. Esketamine has also demonstrated some beneficial effects when used for induction and postoperative analgesia in elderly patients undergoing joint replacement. The present trial differs from those studies by employing only a low-dose intravenous infusion of esketamine during elderly joint replacement surgery. This approach aims to observe its impact on the quality of recovery and to explore the differential effects of various doses, thereby seeking to identify the optimal administration regimen.

Also, this study has several limitations. Firstly, the primary objective was to observe the effects of intravenous infusion of different doses of esketamine on the quality of postoperative recovery in elderly patients undergoing knee arthroplasty. The sample size calculation was primarily based on postoperative recovery quality scores. Our relatively small sample size and single-center design may have resulted in incomplete observation of secondary outcomes, such as postoperative adverse events and anesthetic drug dosages. Therefore, further trials with larger sample sizes are warranted and multicenter trials with extended follow-up periods may be conducted. Secondly, due to time constraints and patient compliance with the assessment scales, this study only collected quality of recovery and related indicators within one week after surgery, and did not use the HADS scale to assess patients' anxiety and depression, which may have led to some bias in the results. We did not perform additional adjustment for baseline QoR-40 in the final analysis. In the future, We plan to introduce the HADS scale, further extend the follow-up period to observe its effect on chronic pain and consider a complementary analysis. Thirdly, the study did not measure the plasma concentration of esketamine or the patients' inflammatory markers. Due to the reduction in total intraoperative opioid consumption in the esketamine groups, the findings of this study cannot distinguish between the direct anti-hyperalgesic effect of esketamine and the indirect benefit resulting from reduced opioid exposure. Future studies with standardized intraoperative opioid dosing are needed to validate its independent effect. Finally, the most effective administration method and dosage of esketamine remain controversial. Although our dosing regimen was demonstrated to be effective, it may not be optimal.

Conclusion

Intraoperative intravenous infusion of esketamine at doses of 0.2 mg/kg/h and 0.3 mg/kg/h improved the quality of recovery to some extent on POD1 in elderly patients undergoing knee arthroplasty. Intraoperative intravenous infusion of esketamine reduced postoperative pain intensity and sleeplessness scores, without causing significant adverse effects.

Data Sharing Statement

The data generated during the current study are available from the corresponding author (Can Fang) upon reasonable request. The study protocol, statistical analysis plan, and clinical study report will also be available.

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Disclosure

The authors report no conflicts of interest related to this work.

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