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Safety and efficacy of low-dose esketamine weakly opioidized anesthesia in elderly patients with lumbar spinal stenosis undergoing surgery: a prospective, double-blind randomized controlled trial

Ni-Na Hou[1†], Meng-Yun Zhang[1†], Yu-Wei Zhang[1†], Hong-Jing Wu[1†], Hong Luo[1*] and Heng Yang[1*]

Abstract

Background The perioperative use of esketamine may reduce opioid use and their adverse effects. We aimed to evaluate the intraoperative safety and efficacy of weak opioidized anesthesia with low-dose esketamine in the treatment of elderly patients with lumbar spinal stenosis undergoing total laminectomy with complete decompression and interbody implant fusion.

Methods In total, 90 elderly patients were randomized into three groups: the esketamine HS group (0.2 mg/kg induction, 0.25 mg/(kg·h) infusion), the esketamine LS group (0.2 mg/kg induction, 0.125 mg/(kg·h) infusion), and the control group (group C receiving an equal volume of saline). The primary outcome was the cumulative dose of sufentanil administered during the perioperative period. Pain (VAS rest and movement scores) on preoperative day 1 (POD-1), postoperative day 1 (POD1), postoperative day 3 (POD3), and postoperative day 7 (POD7), and serum levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-10 (IL-10) on POD-1, POD1, POD3, and POD7 were the secondary outcomes. We also measured mean arterial pressure and the heart rate of the three groups at each time point before anesthesia (T0), immediately after intubation (T1), 5 min after intubation (T2), at the time of surgical skin incision (T3), at the time of extubation (T4), and 30 min after surgery (T5), intraoperative propofol and remifentanil dosage, and the incidence of adverse reactions within 5 days postoperatively, etc.

Results The cumulative perioperative sufentanil dosage and the number of patients undergoing postoperative PACU remedial analgesia were significantly lower in the HS and LS groups compared to the C group ($P < 0.05$). Cumulative perioperative sufentanil use was lower in the HS group compared with the LS group ($P < 0.01$). The VAS dynamic and static pain scores were significantly lower in the HS group at POD1 compared to the C and LS groups. There was no significant difference in VAS dynamic and static pain scores among the three groups at POD3 and POD7 ($P > 0.05$). At POD1, the VAS dynamic and static pain scores were significantly lower in the HS group compared

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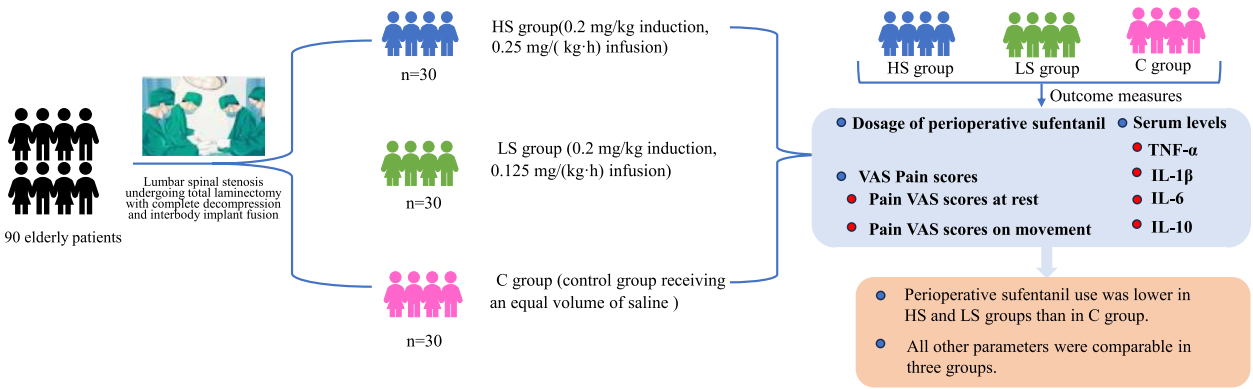
to the C and LS groups. VAS static pain scores were lower in the LS group at POD1 compared to group C ($P < 0.05$), whereas VAS dynamic pain scores did not differ compared to group C ($P > 0.05$). Compared with group C, the serum levels of TNF-α, IL-1β, and IL-6 were significantly lower in the HS and LS groups at POD1, POD3, and POD7. At POD1 and POD3, the serum levels of TNF-α, IL-1β, and IL-6 were lower in the HS group than in the LS group ($P < 0.05$). Serum IL-10 levels were significantly increased at POD1, POD3, and POD7 in the HS and LS groups compared with group C ($P < 0.05$). The incidence of intraoperative hypotension was significantly lower in the HS and LS groups compared with group C ($P < 0.05$). At T2 and T4, the HS and LS groups had significantly lower levels of MAP and HR decline than the C group. At T5, the MAP and HR of the C group were significantly higher than those of the HS and LS groups ($P < 0.05$). The HR at T3 was reduced in the LS group compared with the C and HS groups ($P < 0.05$). The incidence of postoperative respiratory depression was reduced in the HS and LS groups compared to the C group ($P < 0.05$). There was no significant difference between the three groups in terms of postoperative psychiatric adverse reactions, such as hallucinations, nightmares, diplopia, somnolence, and dizziness ($P > 0.05$).

Conclusion Low-dose esketamine is used for its anti-inflammatory and analgesic effects in lumbar spine surgery of elderly patients. It is beneficial to hemodynamic stabilization and can reduce the incidence of postoperative respiratory depression in elderly patients. Among them, 0.2 mg/kg induction and 0.25 mg/(kg-h) infusion were more effective.

Keywords Esketamine, Elderly patients, Lumbar spinal stenosis, Inflammatory factors, Weak opioids

Graphical Abstract



Introduction

Degenerative lumbar spinal stenosis (DLSS) is a common cause of low back pain in the elderly [1]. With the aging process, factors such as long-term weight-bearing labor and incorrect lifestyle can lead to DLSS. An epidemiologic study estimated that approximately 103 million people worldwide are diagnosed with symptomatic DLSS annually [2]. DLSS is mostly caused by the degeneration of intervertebral disc, resulting in intervertebral foraminal stenosis, leading to nerve root and cauda equina compression and adhesion, which leads to several symptoms, such as limited mobility, lumbar back pain, lower limb numbness, etc., and aggravates progressively with the prolongation of the disease course. Chronic pain is one of the main symptoms of DLSS, which seriously affects patients' normal working capacity and quality of life [3].

Surgery has become the treatment of choice for patients with DLSS. Transforaminal laminectomy for complete decompression of intervertebral implant fusion is a long and traumatic procedure, and many opioids are needed for analgesia in the perioperative period. An overdose of opioids often increases the risk of adverse reactions, such as nausea, vomiting, itching, constipation, respiratory depression, etc., which may delay patients' discharge from the hospital and length of recovery [4, 5]. The need for hypo-opioidized anesthesia has been clearly mentioned in the enhanced recovery after surgery (ERAS) concept [6]. Therefore, reducing the amount of opioids and

achieving low-opioid anesthesia while ensuring adequate analgesia has become a goal pursued by clinical anesthesiologists.

Esketamine is the dextro isomer, which possesses almost the same pharmacological effects as ketamine and binds to various receptors, such as NMDA receptors, monoaminergic receptors, and M cholinergic receptors, to induce analgesia, hypnosis, and antidepressant effects. Among them, the sedation and analgesia of esketamine are usually attributed to the non-competitive antagonistic effect of esketamine on the calcium channel pore of the NMDA receptor [7, 8]. Several clinical studies have shown that esketamine reduces opioid consumption and nociceptive sensitization after surgery [9, 10]. Esketamine possesses weaker inhibitory effect on the respiratory and circulatory systems [11], and can theoretically be used to provide the analgesic effects of opioids while preventing opioid-related adverse effects. Small doses of esketamine have been shown to possess favorable analgesic effects [12]. However, there is less data on the effects of low-dose esketamine on intraoperative anesthesia and postoperative pain in elderly patients with lumbar spinal stenosis.

Therefore, we used weak opioid anesthesia with a small dose of esketamine to assess its effect on the treatment of lumbar spinal stenosis in elderly patients undergoing complete decompression interbody implant fusion via total laminectomy.

Material and methods

Study design and ethics

This prospective, double-blind, randomized controlled trial was approved by the Human Research Ethics Committee of the Third Affiliated Hospital of Anhui Medical University on March 28, 2022 (Approval No.: 2022–021-01, Principal Investigator: Professor Luo). It has been registered in the China Clinical Trial Registry (registration number: ChiCTR2200066896, Principal Investigator: Hong Luo, registration date: December 21, 2022). The protocol was explained to patients and written informed consent was obtained from all participants before starting the trial. All procedures were conducted following relevant guidelines and regulations. We followed the Consolidated Standards for Reporting Trials (CONSORT) reporting guidelines (Fig. 1).

Participants

The trial enrolled patients aged 65 to 89 years with an American Society of Anesthesiologists (ASA) physical status classification of II to III (I for healthy patients, II for patients with mild systemic disease, III for patients with severe systemic disease, and IV for those with severe systemic disease with a stage of loss of function). We included elderly patients with lumbar spinal stenosis who visited the Department of Spine and Orthopaedics of the Third Affiliated Hospital of Anhui Medical University between December 2022 and February 2024 and were treated with total laminectomy and complete

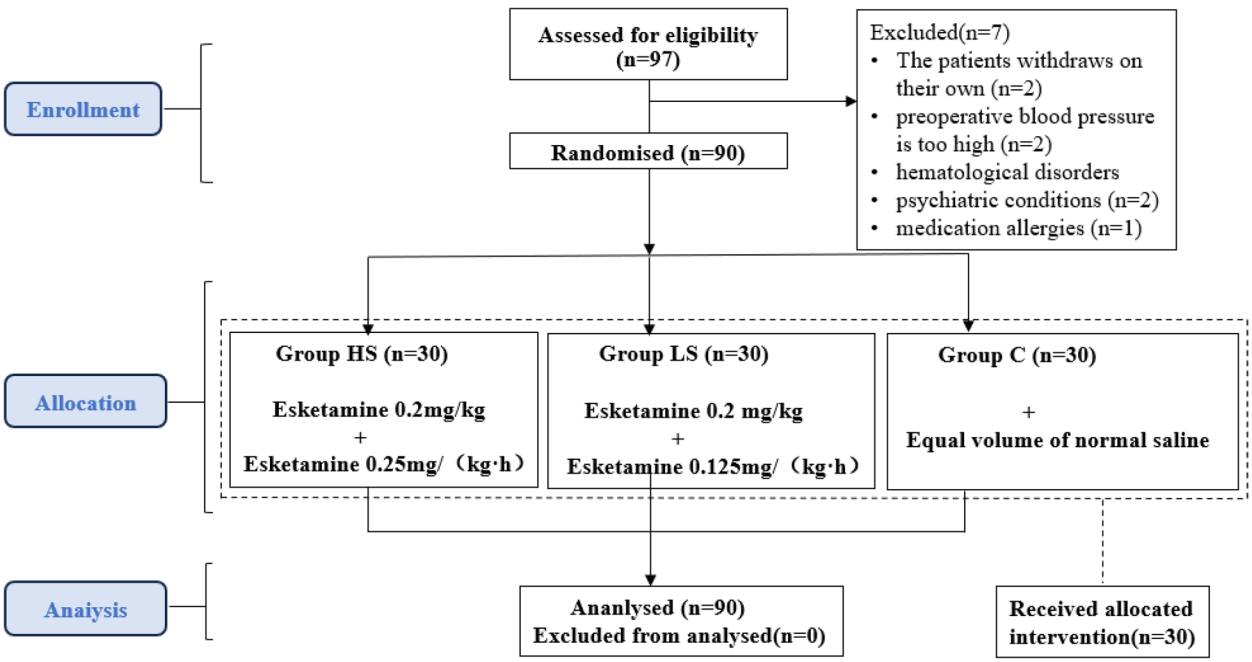


Fig. 1 CONSORT patient enrolment diagram. CONSORT, Consolidated Standards of Reporting Trials

decompression interbody implant fusion under general anesthesia. All participants were included after signing a written informed consent form.

The inclusion criteria were as follows: (1) age between 65 and 89 years; (2) imaging showing definite manifestations of lumbar spinal stenosis; and (3) patients successfully completed surgery.

The exclusion criteria were as follows: (1) patients refused to participate in this study; (2) hypersensitivity or contraindication for esketamine or other drugs routinely used intraoperatively; (3) patients with significant preoperative neuropsychiatric and cognitive disorders; (4) those with severe respiratory-circulatory disorders; (5) those with severe hepatic or renal dysfunction; (6) patients with severe and poorly controlled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg).

Randomization and blinding

During the preoperative visits, the investigators obtained detailed information about patients' physical condition and basic information (including gender, age, height, weight, and years of schooling, etc.).The experimental protocol was explained to the patients and their families, and written informed consent was signed by the patients and their legal guardians. One day before surgery (POD-1), two researchers collected 3 ml of venous blood from the patients (collected at 6–7 am). The patients were assessed for preoperative pain using pain visual analog scale (VAS). SPSS 26.0 software (IBM SPSS, Armonk, NY, USA) randomly assigned all participants in a ratio of 1:1:1 into the esketamine group (HS group), esketamine (LS group), and control group (C group). Nurse anesthetists completed the randomization and treatment assignment the morning before surgery. Nurses prepared the drugs by grouping and calculated the dose of esketamine (2 ml: 50 mg, Hengrui Induction, Jiangsu, China) for anesthesia induction and maintenance based on patients' body weight. Esketamine was diluted to 5 ml in saline for induction and diluted to 20 ml in saline for maintenance. It was kept in opaque, sterile anesthetic syringe Tray, and was then given to the hands of the anesthesiologist on duty that day. Patients, anesthesiologists, nurse anesthetists, and investigators responsible for patient recruitment, data collection, and follow-up assessment were blinded to clusters.

Anesthesia and perioperative analgesia management

The patients were routinely fasted and abstained from food and drink for 8 h preoperatively. After entering the operation room, a peripheral vein was opened and infused with lactated Ringer's solution. Electrocardiogram, pulse oximetry, invasive blood pressure (BP), carbon dioxide waveform, inhalation anesthetic concentration, electroencephalographic bifrequency index (BIS), nasopharyngeal temperature, and urine output were intraoperatively monitored.

The HS and LS groups received esketamine (0.2 mg/kg) as induction medication, whereas saline was used in group C. Subsequently high-dose esketamine (0.25 mg/(kg-h)) was used as the maintenance drug in the HS group, low-dose esketamine (0.125 mg/(kg-h)) was used as the maintenance drug in the LS group, and an equal volume of saline was used to maintain anesthesia in the C group. Other procedures were the same in the three groups.

Anesthesia was induced by intravenous infusion of penehyclidine Hydrochloride Injection (0.2 mg), dexamethasone (10 mg), midazolam (0.03 mg/kg), etomidate (0.2 mg/kg), sufentanil (0.3 μg/kg), and cis-atracurium (0.2 mg/kg). Tracheal intubation was performed under visual laryngoscopy when the patient was unconscious and the jaw was relaxed. Mechanical ventilation was done after intubation. End-expiratory CO2 pressure (PetCO 2) was maintained between 35 and 45 mmHg by adjusting tidal volume (6–8 mL/kg) and respiratory rate (12–14 breaths/min). Subsequently, remifentanil (6–18 μg/(kg-h)) and propofol (3-6 mg/(kg-h)) were infused to maintain anesthesia, BIS was maintained at 40–60, and sufentanil was infused intermittently at 5–10 ug/dose based on the BIS value. The indexes of BP and HR parameters, and the BP and HR were maintained at ± 20% of the basal value. If they exceeded this threshold, vasoactive drugs were given when needed. Cisatracurium (1–2 mg) was pushed intermittently as needed for the procedure. Esketamine and saline were discontinued at the time of surgical suturing. Propofol and remifentanil were discontinued at the end of the procedure. After the patient regained consciousness and confirmed that the patient responded rapidly to verbal commands, the airway protective reflexes recovered well, the voluntary tidal volume was > 6 ml/kg, and the respiratory rate was smooth and regular. The endotracheal tube was withdrawn, and the patient was transferred to the PACU for monitoring. If the visual analog scale (VAS) of pain was ≥ 4 points, sufentanil was given (0.1 μg/kg), and if the pain was not relieved for 30 min, sufentanil was given at 0.05 μg/kg. When the patients had the modified Aldrete score (with a total score of 0–10. A score of 10 indicated the best possible clinical condition) ≥ 9 [13], they were returned to the general ward. All patients were connected to an patient controlled intravenous analgesia (PCIA) device for postoperative in-ward analgesia, which was configured using 100 μg sufentanil + 100 μg dexmedetomidine + 20 mg metoclopramide hydrochloride + saline in

a total volume of 150 mL, with no background dosage, a single dose of 2 mL, and a lockout time of 15 min.

Intraoperative hypotension was defined as a decrease in MAP of more than 20% from the preoperative level, and intraoperative hypertension was defined as an increase in MAP of more than 20% from the preoperative level or a systolic blood pressure of > 180 mm Hg. Dobutamine 2 mg/dose was given in case of intraoperative hypotension, and uradil 10 mg/dose was given in case of hypertension. Atropine 0.3 mg/dose/minute was applied for heart rate less than 50 beats, and esmolol 10 mg/dose/minute was applied for a heart rate more than 100 beats.

Outcome measures

The primary outcome was the dose of sufentanil used in the perioperative period (cumulative PCIA dosage from the induction of anesthesia to 72 h postoperatively). Patient pressed the intravenous self-contained analgesia device on demand with a single dose of 2 ml). Secondary outcomes were as follows: the concentrations of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10) serum biomarker at 1 day preoperatively (POD-1), postoperative day 1 (POD1), postoperative day 3 (POD3), and 7 days postoperatively (POD7) (POD refers to the perioperative period), mean arterial pressure and heart rate of each group at each time point before anesthesia (T0), immediately after intubation (T1), 5 min after intubation (T2), at the time of surgical incision (T3), at the time of extubation (T4), and 30 min after surgery (T5), frequency of intraoperative vasoactive drug use, the visual analog scale (VAS) of pain at rest and during exercise (with a score of 0 indicating no pain and a score of 10 indicating severe pain) [14] on POD-1, POD1, POD3, and POD7, intraoperative bleeding, urine output, fluid replacement volume, operative time, anesthesia time, awaking time, PACU stay,extubation time, propofol and remifentanil dosage, postoperative hospital stay, and the incidence of adverse events within 5 days after surgery (respiratory depression (pulse oximetry < 90%), nausea, vomiting, and psychiatric adverse effects (hallucinations, nightmares, diplopia, somnolence, dizziness, etc.).

Measurement of serum biomarkers: 3 ml of venous blood was collected, and centrifuged at 1000 rpm for 10 min within 15 min. The supernatant was collected and stored at -80 °C. Serum biomarkers were measured using ELISA. The concentrations of TNF-α, IL-1β, IL-6, and IL-10 in the peripheral blood were measured by ELISA. All steps were conducted strictly following the instructions of the ELISA kit (Shanghai Jianglai Biotechnology Co., Ltd., Shanghai, China).

Sample size calculation

In this study, the sample size was calculated using perioperative sufentanil use as the main indicator. The sample size of all three groups was designed as 1:1:1, and SPSS 26.0 software was utilized for sample size calculation. Based on the results of the pilot study, the mean sufentanil dosage was 60.42 μg, 65.67 μg, and 70.28 μg in groups HS, LS, and C, respectively, and the standard deviation was set to ± 9.54. We considered ß = 0.1 and α = 0.05 for power analysis. In addition, we considered 10% shedding, exclusion factors and the need for safety observations, it was estimated that 84 patients needed to be included and 97 patients were finally included.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software. The normal distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Continuous data are expressed as mean (SD) and compared using one-way ANOVA. Non-normally distributed data were analyzed using the Kruskal–Wallis test and reported as median (IQR). Categorical variables are expressed as the number of patients (n%) and were processed using the chi-square test or Fisher exact probability test. Comparisons between multiple groups were conducted using one-way ANOVA plus two-way LSD-t test. Repeated observations were analyzed using repeated measures ANOVA. Two-by-two intergroup comparisons were conducted using LSD-t test, and two-by-two time comparisons were conducted using t-test. Two-sided α = 0.05 was considered for interpreting differences. Repeated-measures analysis and split test for multiple comparisons were adjusted to the test level following the Bonferroni correction method. p-value < 0.05 was considered statistically significant.

Results

Enrolled patients

In total, 97 participants were recruited in this study. Five participants did not meet the inclusion criteria, 2 withdrew from the study, and 90 completed the study (Fig. 1). The 90 patients were randomly assigned to three groups (n = 30 per group).

Demographic characteristics

There were no significant differences in demographic data, such as age, gender, body mass index, ASA classification, preoperative comorbidities, smoking, drinking status, and education level among the three groups (P > 0.05, Table 1).

Table 1 Patients' demographic and baseline characteristics

	Group HS ($n=30$)	Group LS ($n=30$)	Group C ($n=30$)	*P* value
Age [years, mean (SD)]	75.55 (4.23)	74.93 (4.89)	73.96 (6.36)	0.498
Sex [n(%)]				
Male	16 (53.33)	14 (46.67)	17 (56.66)	0.732
Female	14 (46.67)	16 (53.33)	13 (43.34)	
BMI [kg/m2, mean (SD)]	25.64 (3.06)	24.78 (2.70)	24.15 (3.26)	0.614
Smoking [n(%)]	12 (40.00)	11 (36.67)	12 (40.00)	0.954
Alcoholism [n(%)]	17 (56.66)	15 (50.00)	17 (56.66)	0.836
Education level [n(%)]				0.461
Junior high school and below	25 (83.33)	28 (93.33)	26 (86.66)	
High school education and above	5 (16.67)	2 (6.67)	4 (13.34)	
ASA [n(%)]				0.435
II	24 (80.00)	22 (73.34)	26 (86.66)	
III	6 (20.00)	8 (26.66)	4 (13.34)	
Preoperative comorbidities [n(%)]				
Coronary heart disease	1 (3.33)	0 (0.00)	1 (3.33)	0.439
Hypertension	20 (66.66)	24 (80.00)	24 (80.00)	0.382
Diabetes mellitus	2 (6.66)	2 (6.66)	2 (6.66)	1.000
Cerebral infarction	4 (13.33)	3 (10.00)	6 (20.00)	0.538

Data are presented as mean (SD), number (percentage). Age and BMI were analyzed using one-way ANOVA, while sex, smoking, alcoholism, education level, ASA, and preoperative comorbidities were compared using chi-square or Fisher's exact probability test

Abbreviations: *ASA* American Society of Anesthesiologists, *BMI* body mass index, *HS* high-dose esketamine group, *LS* low-dose esketamine group and *C* control group

Clinical and surgical characteristics

Comparing the surgical site, intraoperative rehydration volume, intraoperative blood loss, urine volume, operation time, and anesthesia time among the three groups, there was no significant difference between the three groups. However, the awakening time, extubation time, and length of stay in PACU were significantly shorter in HS and LS groups than in C group ($P<0.01$, Table 2).

Dosage of perioperative sufentanil and intraoperative propofol and remifentanil

The cumulative perioperative sufentanil dosage, intraoperative sufentanil dosage, number of postoperative PACU remedial analgesia cases, sufentanil remedial analgesia dosage, and the dosage of sufentanil used in the postoperative PCIA at 72 h after surgery were significantly lower in the HS and LS groups compared to the C group ($P<0.01$). The cumulative use of perioperative sufentanil and intraoperative dose of sufentanil were lower in the HS group compared to the LS group ($P<0.01$). Intraoperative consumption of propofol and remifentanil was significantly lower in the HS and LS groups compared to the C group ($P<0.01$) Table 3.

Hemodynamic indexes

The incidence of intraoperative hypotension and the number of patients using vasopressors (dobutamine) were significantly reduced in the HS and LS groups compared to group C($P<0.05$).

There was no significant difference in the incidence of intraoperative hypertension, tachycardia, and bradycardia between the three groups ($P>0.05$, Table 4).

Compared to T0, the three groups had significantly lower MAP and HR at T2, T3, and T4, and significantly higher HR at T5. The HS and LS groups exhibited significantly smaller decline in MAP and HR compared to the C group at T2 and T4. At T5, the MAP and HR of group C were significantly higher than those of the HS and LS groups ($P<0.05$). Compared to the C and HS groups, the LS group showed a significant decrease in HR at T3 ($P<0.05$, Fig. 2).

Pain scores

There was no significant difference in terms of VAS resting and movement pain scores at POD-1 among the three groups ($P>0.05$). Compared to POD-1, VAS resting and movement pain scores at POD1, POD3, and POD7 were lower in all groups ($P<0.05$). The VAS resting and movement pain scores were significantly lower in the HS group at POD1 compared to the C and LS groups ($P<0.05$). Compared to group C, the LS group had lower VAS resting pain scores at POD1 ($P<0.05$), but there was no difference in VAS movement pain scores compared to group C ($P>0.05$) (Fig. 3).

Table 2 Clinical characteristics of patients in the three groups

	Group HS ($n=30$)	Group LS ($n=30$)	Group C ($n=30$)	*P* value
Surgical segments [n(%)]				
L_{1-2}	0 (0.00)	1 (3.33)	0 (0.00)	0.905
L_{2-3}	6 (20.00)	5 (16.66)	5 (16.66)	
L_{3-4}	8 (26.66)	9 (30.00)	7 (23.33)	
L_{4-5}	14 (46.66)	12 (40.00)	16 (53.33)	
L_{5-S}	2 (6.67)	3 (10.00)	2 (6.67)	
Fluid infusion volume [ml,mean (SD)]	887.45 (78.2)	896.92 (77.5)	907.84 (65.6)	0.567
Blood loss [ml, mean (SD)]	58.62 (14.41)	55.92 (15.00)	60.18 (13.57)	0.510
Urine output [ml, mean (SD)]	250 (60)	260 (80)	280 (45)	0.055
Surgical duration [min, mean (SD)]	193.50 (43.88)	214.80 (53.39)	201.10 (57.94)	0.281
Anesthesia duration [min, mean (SD)]	229.97 (50.64)	248.41 (49.95)	234.79 (64.68)	0.414
Awaking time [min, mean (SD)]	4.95 (2.20)[b]	5.16 (2.66)[b]	9.54 (3.08)	< 0.01
Extubation time [min, mean (SD)]	4. 35 (1. 70)[b]	3. 76 (1. 53)[b]	7. 54 (1.73)	< 0.01
PACU stay [min, mean (SD)]	18.84 (5.35)[b]	19.14 (5.79)[b]	25.72 (7.44)	< 0.01

Data are presented as mean (SD), number (percentage). Surgical segments metrics were compared using the chi-square test or Fisher's exact probability test, while fluid infusion volume, blood loss, urine output, surgical duration, anesthesia duration, awaking time, extubation time, and PACU stay were analyzed using one-way ANOVA

Abbreviations: L_{1-2} first lumbar vertebra to second lumbar vertebrae, L_{2-3} s lumbar vertebra to third lumbar vertebrae, L_{3-4} third lumbar vertebra to fourth lumbar vertebrae, L_{4-5} fourth lumbar vertebra to fifth lumbar vertebrae, L_{5-S} fifth lumbar vertebra to sacrum, *HS* high-dose esketamine group, *LS* low-dose esketamine group and *C* control group

[b] $p<0.05$ vs. the C group at the same time

Table 3 Perioperative sufentanil and intraoperative doses of propofol and remifentanil

	Group HS ($n=30$)	Group LS ($n=30$)	Group C ($n=30$)	*P* value
Intraoperative dose of sufentanil [ug, mean (SD)]	26.33 (5.41)[ab]	30.62 (4.84)[b]	35.92 (5.27)	< 0.01
The cases of postoperative PACU sufentanil remedial analgesia [n(%)]	2 (6.67)[b]	3 (13.33)[b]	10 (33.33)	0.010
Sufentanil salvage analgesic dose, at PACU[ug, mean (SD)]	5.58 (1.23)[b]	7.28 (3.91)[b]	12.72 (5.21)	< 0.01
Sufentanil salvage analgesic dose, with PCIA (72 h) [ug, mean (SD)]	25.75 (6.03)[b]	27.37 (6.42)[b]	33.69 (8.05)	< 0.01
Cumulative dose of sufentanil in the perioperative period [ug, mean (SD)]	58.45 (11.61)[ab]	65.73 (14.31)[b]	83.25 (18.71)	< 0.01
Propofol dose [mg, mean (SD)]	704.15 (205.39)[b]	764.15 (233.72)[b]	883.26 (229.02)	0.009
Remifentanil dose [mg, mean (SD)]	0.92 (0.32)[b]	0.99 (0.45)[b]	1.34 (0.47)	< 0.01

Data are presented as mean (SD), number (percentage). The cases of postoperative PACU sufentanil remedial analgesia were compared using chi-square test or Fisher's exact probability test, while intraoperative dose of sufentanil, sufentanil salvage analgesic dose at PACU, sufentanil salvage analgesic dose with PCIA (72 h), cumulative dose of sufentanil in the perioperative period, propofol dose, and remifentanil dose were analyzed using one-way ANOVA

Abbreviations: *PACU* post-anesthesia care unit, *PCIA* patient-controlled intravenous analgesia, *HS* high-dose esketamine group, *LS* low-dose esketamine group and *C* control group

[a] $p<0.05$ vs. LS group at the same time

[b] $p<0.05$ vs. C group at the same time

Serum levels of TNF-α, IL-1β, IL-6 and IL-10

The serum levels of TNF-α, IL-1β, IL-6, and IL-10 at POD-1 was not significantly different among the three groups ($P>0.05$, Fig. 4).

Compared to POD-1, the serum levels of TNF-α were elevated in group C at POD1, POD3, and POD7 ($P<0.05$), whereas the serum levels of TNF-α were elevated in groups HS and LS only at POD1 and POD3 ($P<0.05$). Compared with group C, serum TNF-α levels were decreased in HS and LS groups at POD1, POD3, and POD7 ($P<0.05$). Compared with the LS group, it was significantly lower in the HS group at POD1 and POD3 ($P<0.05$, Fig. 4A).

Compared to group C, the serum levels of IL-1β and IL-6 were significantly lower in the HS and LS groups at POD1, POD3, and POD7. The decrease was more pronounced in the HS group than in the LS group at POD1 and POD3 ($P<0.05$). Compared to POD-1, the serum levels of IL-1β and IL-6 were significantly reduced in HS and LS groups at POD7 ($P<0.05$, Fig. 4B, C).

Table 4 The clinical characteristics of patients among the three groups

	Group HS ($n=30$)	Group LS ($n=30$)	Group C ($n=30$)	*P* value
Vasopressor used [n(%)]	3 (10.00)[b]	4 (13.33)[b]	10 (33.33)	0.044
Hypotension [n(%)]	5 (16.66)[b]	5 (16.66)[b]	13 (43.33)	0.024
Hypertension [n(%)]	5 (16.66)	2 (6.67)	4 (13.33)	0.461
Bradycardia [n(%)]	2 (6.67)	3 (10.00)	2 (6.67)	0.861
Tachycardia [n(%)]	1 (3.33)	0 (0.00)	2 (16.66)	0.242

Data are presented as number (percentage). Vasopressor used, hypotension, hypertension, bradycardia, and tachycardia using the chi-square test or Fisher's exact probability test

Abbreviations: *Vasopressors*: dopamine, *HS* high-dose esketamine group, *LS* low-dose esketamine group and *C* control group

[b] $p<0.05$ vs. the C group at the same time

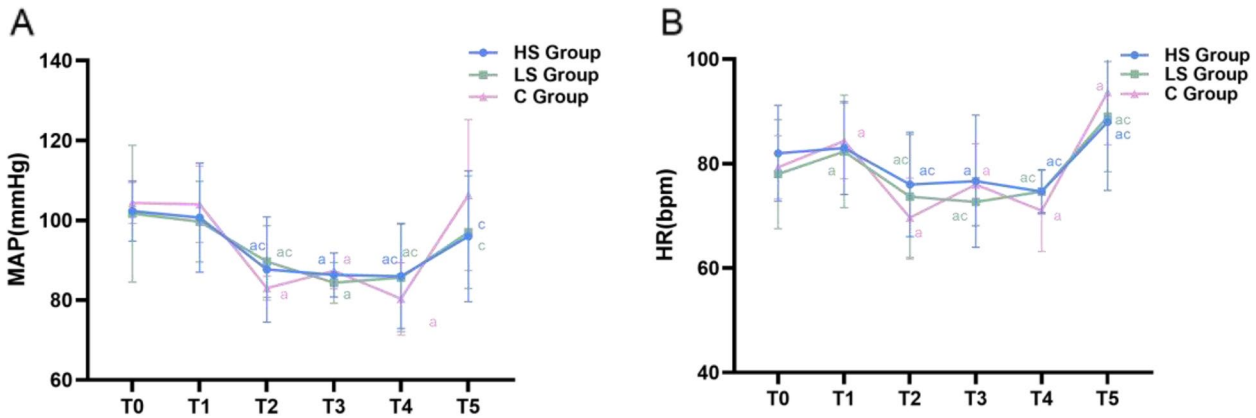


Fig. 2 Comparison of hemodynamic indexes between the three groups. Note: Data are presented as mean (SD). Overall comparisons were conducted using two-factor repeated-measures ANOVA with sphericity correction by the HF coefficient method. Fine comparisons at latitude between groups were conducted using LSD-t tests. Fine comparisons at time (within group) latitude were conducted using t-tests (the Bonferroni correction method). [a]$p<0.05$ vs. the same group at T0. [b]$p<0.05$ vs. the LS group at the same time; [c]$p<0.05$ vs. the C group at the same time. Abbreviations: MAP: mean arterial pressure; HR: heart rate; T0: before anesthesia; T1: immediate intubation; T2: 5 min after intubation; T3: at the time of surgical skin incision; T4: at extubation; T5: 30 min postoperatively; HS: high-dose esketamine group; LS: low-dose esketamine group and C: control group

Compared with POD-1, the serum levels of IL-10 were decreased in all three groups at POD1, POD3, and POD7 ($P<0.05$). The serum levels of IL-10 were increased at POD1, POD3, and POD7 in the HS and LS groups compared to group C ($P<0.05$, Fig. 4D).

Incidence of adverse events and time to discharge within 5 days postoperatively

Compared with group C, the discharge time was significantly shorter in the HS and LS groups ($P<0.01$). Compared with group C, the risk of respiratory depression was significantly lower in the HS and LS groups ($P<0.05$), but there was no significant difference between the HS and LS groups ($P>0.05$). There was no significant difference ($P>0.05$) between the three groups in terms of postoperative nausea, vomiting, constipation, and psychiatric adverse reactions, such as hallucinations, nightmares, diplopia, somnolence, and dizziness ($P>0.05$, Table 5).

Discussion

Transforaminal laminectomy with complete decompression and intervertebral implant fusion is an option for the surgical treatment of patients with lumbar spinal stenosis. Due to its long and traumatic surgical time, most patients usually suffer from acute pain [15]. Due to the poorer tolerance of elderly patients, the incidence of adverse reactions, such as hypotension and respiratory depression, is higher with opioids, which greatly reduces the quality of postoperative recovery and exacerbates the risk of debilitation [16]; thus, low-dose opioid anesthesia is of great significance for this population.

Esketamine is a dextrose isolated from ketamine, with a greater potency and stronger analgesic effect, about twice as much as conventional ketamine. Therefore, esketamine is administered in smaller doses and has weaker side effects [17]. Esketamine and opioids possess different analgesic mechanisms; thus, the use of esketamine as

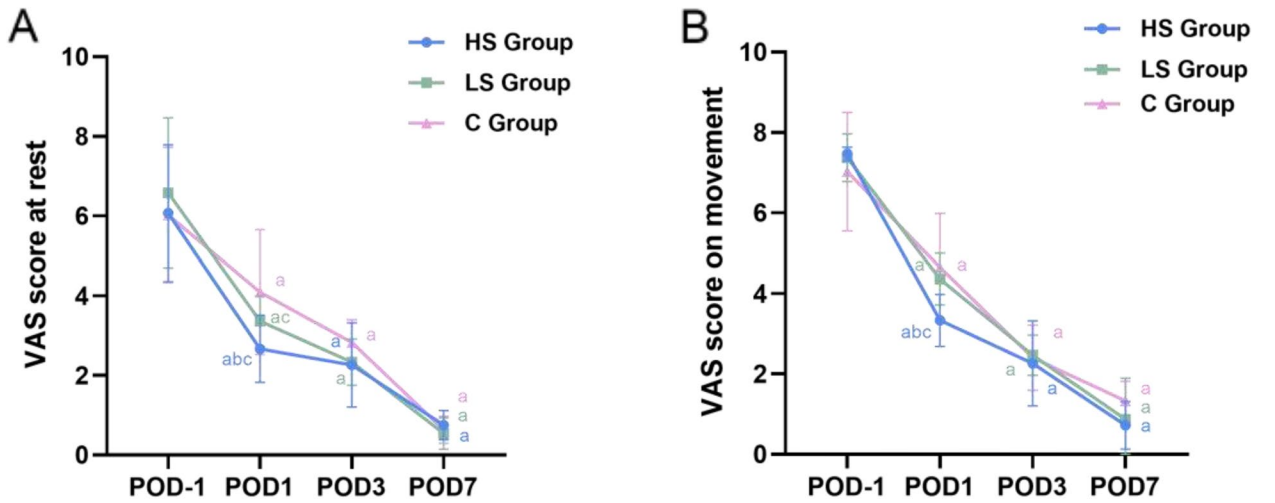


Fig. 3 Pain VAS scores at rest and pain VAS scores on movement among the three groups. Note: Data are presented as median (IQR). Overall comparisons were conducted using two-factor repeated-measures ANOVA with sphericity correction by the HF coefficient method. Fine comparisons at latitude between groups were conducted using LSD-t tests. Fine comparisons at time (within group) latitude were conducted using t-tests (the Bonferroni correction method). [a]$p < 0.05$ vs. the same group at POD-1. [b]$p < 0.05$ vs. the LS group at the same time; [c]$p < 0.05$ vs. the C group at the same time. Abbreviations: VAS: visual analogue scale; POD refers to the perioperative period. POD-1: 1 day before surgery; POD1: postoperative day 1; POD3: postoperative day 3; POD7: postoperative day 7; HS: High-dose esketamine group; LS: Low-dose esketamine group and C: control group

a partial replacement for opioids is consistent with the concept of multimodal analgesia [18]. It has been shown that an intravenous push of 0.5 mg/kg esketamine immediately after the induction of anesthesia, followed by a continuous intravenous infusion at a rate of 0.25 mg/(kg-h) can significantly reduce patients' morphine consumption over the 24 h after the surgery [19]. However, esketamine at this dose may increase the risk of adverse effects, such as dizziness, hallucinations, and increased secretions [20]. Side effects of esketamine are generally dose-dependent and may not be clinically important when applied in small doses [21]. Wang et al. [11] showed that 0.2 mg/kg esketamine may be an appropriate dose for the induction of anesthesia in elderly patients. We therefore chose a smaller dose of 0.2 mg/kg esketamine for induction and a continuous infusion of 0.25 mg/(kg-h) esketamine or 0.125 mg/(kg-h) esketamine, respectively. In the present study, we found that esketamine significantly reduced the cumulative perioperative dose of sufentanil, effectively relieved the postoperative resting and movement VAS scores on POD1, POD3, and POD7. In particular, esketamine (0.2 mg/kg induction, 0.25 mg/(kg-h) infusion) reduced perioperative sufentanil dosage and improved early postoperative pain, which may be associated with the analgesic properties of esketamine in a dose-dependent manner.

Esketamine mildly depresses respiration and has mild excitatory effects on the circulatory system, mildly increasing blood pressure and heart rate [22, 23]. Elderly patients have a fragile cardiovascular system, with a very high incidence of hypotension after inducing anesthesia [24]. Perioperative hypotension is closely associated with a series of serious complications, such as postoperative myocardial injury, acute kidney injury, and postoperative delirium [25]. The stimulating effects of esketamine on the cardiovascular system may help reduce the risk or severity of intraoperative hypotension [26] and decrease the risk of complications. In this study, we found that esketamine can significantly reduce the risk of intraoperative hypotension. The levels of MAP and HR decline in HS and LS groups were significantly lower than those in C group at T2 and T4. In contrast, at T5, MAP and HR in the C group were significantly higher than those in the HS and LS groups ($P < 0.05$). These findings suggest that intraoperative use of esketamine is more conducive to hemodynamic stabilization in elderly patients. Esketamine has excitatory effects on the sympathetic center and the cardiovascular system [27], thereby counteracting the circulatory depressant effects of some anesthetic drugs.

Our results showed that in elderly patients with lumbar spinal stenosis undergoing complete decompression interbody implant fusion via total laminectomy, low-dose esketamine can relieve patients' early postoperative pain, reduce the perioperative dose of sufentanil, improve intraoperative circulatory stability of elderly patients, reduce the risk of postoperative respiratory depression, without increasing the risk of adverse events, such as psychiatric symptoms, in the first 5 days after surgery.

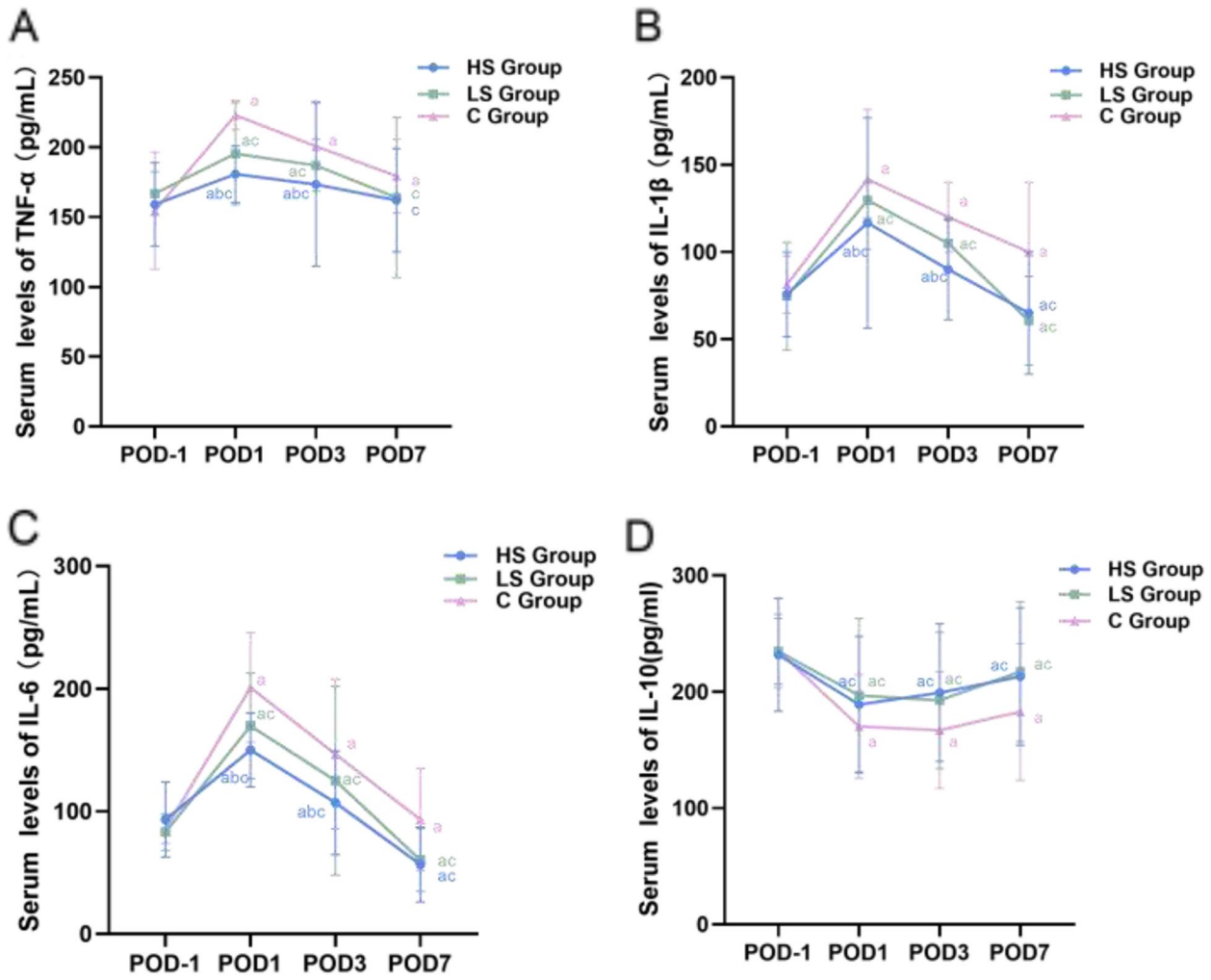


Fig. 4 Changes in the levels of perioperative biomarkers among the three groups. Note: Data are presented as mean (SD). Overall comparisons were conducted using two-factor repeated-measures ANOVA with sphericity correction by the HF coefficient method. Fine comparisons at latitude between groups were conducted using LSD-t tests. Fine comparisons at time (within group) latitude were conducted using t-tests (the Bonferroni correction method). $^{a}p < 0.05$ vs. the same group at POD-1. $^{b}p < 0.05$ vs. the E2 group at the same time. $^{c}p < 0.05$ vs. the C group at the same time. Abbreviations: TNF-α: tumor necrosis factor α; IL-1β: interleukin 1β; IL-6: interleukin 6; IL-10: interleukin 10. POD refers to the perioperative period. POD-1: 1 day before surgery; POD1: postoperative day 1; POD3: postoperative day 3; POD7: postoperative day 7; HS: high-dose esketamine group; LS: low-dose esketamine group and C: control group

Low-dose esketamine can also accelerate patient discharge, particularly when using esketamine 0.2 mg/kg as induction and 0.25 mg/(kg-h) as an infusion.

Studies have shown that surgical trauma can induce local inflammation, especially after orthopedic surgery [28]. Subsequently, microglia differentiate into M1 and M2 types. The former produces pro-inflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), whereas the latter produces anti-inflammatory cytokines, such as interleukin-10 (IL-10). Cellular inflammatory factors, such as IL-1β, IL-6, and TNF-α induce pain and peripheral sensitization by interacting with sensory neurons [29]. The present study indicated that the concentrations of TNF-α, IL-1β, and IL-6 were elevated at POD1 and POD3, and the concentrations of IL-10 were decreased in all three groups of patients compared to POD-1. These findings shows that surgical stimulation has a great effect on TNF-α, IL-1β, IL-6, and IL-10 concentrations. Ketamine can inhibit the activation of leukocytes, reduce the production of inflammatory cytokines TNF-α, IL-1β, and IL-6, and stimulate the secretion of anti-inflammatory factors interleukin-4 and interleukin-10 to alleviate the inflammatory response [30].

Table 5 Postoperative adverse reaction rates and time to discharge

	Group HS ($n=30$)	Group LS ($n=30$)	Group C ($n=30$)	*P* value
Postoperative data				
Length of hospital stay after surgery [day, mean (SD)]	8.24 (1.77)[a]	8.08 (2.60)[a]	10.95 (2.32)	< 0.01
Incidence of adverse reactions within 5 days after surgery [n(%)]				
Nausea or vomiting [n(%)]	3 (10.00)	1 (3.33)	2 (6.67)	0.572
Constipation [n(%)]	0 (0.00)	1 (3.33)	1 (3.33)	0.439
Respiratory depression [n(%)]	0 (0.00)[a]	2 (6.67)[a]	5 (16.67)	0.001
Pruritus [n(%)]	0 (0.00)	0 (0.00)	1 (3.33)	0.330
Psychiatric symptoms				
Hallucination [n(%)]	2 (6.67)	3 (10.00)	2 (6.67)	0.861
Nightmare [n(%)]	1 (3.33)	2 (6.67)	2 (6.67)	0.794
Diplopia [n(%)]	2 (6.67)	1 (3.33)	0 (0.00)	0.242
Drowsiness [n(%)]	1 (3.33)	0 (0.00)	1 (3.33)	0.439
Dizziness [n(%)]	0 (0.00)	0 (0.00)	1 (3.33)	0.330

Data are presented as mean (SD), number (percentage). The incidence of adverse reactions within 5 days after surgery, nausea or vomiting, constipation, respiratory depression, pruritus, hallucination, nightmare, diplopia, drowsiness, and dizziness were compared using the chi-square test or Fisher's exact probability test, while the length of hospital stay after surgery was analyzed using one-way ANOVA

Abbreviations: *HS* high-dose esketamine group, *LS* low-dose esketamine group and *C* control group

[a] $p < 0.05$ vs. the C group at the same time

Esketamine has the same anti-inflammatory effects as ketamine [31, 32]. In this study, intraoperative use of esketamine was found to inhibit the expression of serum TNF-α, IL-1β, and IL-6 and promote the expression of IL-10 at 1, 3, and 7 postoperative days. The reduction in inflammatory cytokines was especially pronounced with esketamine infusion (0.2 mg/kg induction, 0.25 mg/(kg-h)). In addition, the trends of inflammatory factors were consistent with the trends of resting and active VAS pain scores. Therefore, the present study suggests that esketamine may improve postoperative pain of elderly patients by inhibiting the expression of pro-inflammatory factors TNF-α, IL-1β, and IL-6 in the peripheral serum and promoting the release of the anti-inflammatory factor IL-10.

Limitations

This study has some limitations. First, we only assessed the incidence of a few adverse effects of esketamine, such as hallucinations, nightmares, diplopia, somnolence, and dizziness. Esketamine may lead to adverse reactions, such as blurred consciousness and disorientation, which necessitates further studies. Second, the follow-up time of this study was short, which should be extended in future studies. Patients' postoperative life satisfaction should be assessed with the Quality of Recovery-15 (QoR-15) scale. Third, this study was conducted only in our hospital, and a few participants were included. Future studies should address these deficiencies to guide clinical practice.

Conclusion

Esketamine effectively relieved early postoperative pain in elderly lumbar spinal stenosis patients undergoing complete decompressive interbody implant fusion via total laminectomy, reduced the dose of perioperative sufentanil, decreased the risk of postoperative respiratory depression, maintained intraoperative hemodynamic stabilization, and improved perioperative safety. Esketamine also decreased the serum levels of proinflammatory factors TNF-α, IL-1β, and IL-6, and promoted the release of the anti-inflammatory factor IL-10. It did not increase the risk of adverse events within 5 days after surgery. Moreover, it accelerated patients' discharge, particularly when using esketamine 0.2 mg/kg as the induction and when using 0.25 mg/(kg-h) as the infusion.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Declarations of interest

None.

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Data availability
All necessary data supporting our findings have been presented within the manuscript. The datasets used and/or analyzed during the current study are available for anyone who wishes to access them for reasonable request. The date will be accessible from the corresponding author.

Declarations

Ethics approval and consent to participate
The authors declared that all the study patients provided written informed consent and that this study was conducted in accordance with the Declaration of Helsinki. This trial was approved by the ethics committee of the current hospital (No. 2022–021-01).

Consent for publication
All the authors have read this article and gave agreements to publish it.

Competing interests
The authors declare no competing interests.

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