British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(3): 51728
https://doi.org/10.31083/BJHM51728

Article

The Effect of Esketamine on Postoperative Fatigue Syndrome in Middle-Aged and Elderly Patients Undergoing Lumbar Vertebral Body Fusion Surgery—A Retrospective Study

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Academic Editor: John Alcolado
Submitted: 1 April 2025 Revised: 12 June 2025 Accepted: 16 June 2025 Published: 11 March 2026

Abstract

Aims/Background: Lumbar spine disease frequently occurs in middle-aged and elderly individuals, significantly affecting their physical and mental health. Posterior lumbar interbody fusion (PLIF) is widely used for treating these diseases; however, postoperative complications may lead to fatigue. Therefore, we explore the effect of different postoperative doses of esketamine on postoperative fatigue syndrome (POFS) in patients undergoing PLIF. **Methods**: This retrospective study analyzed the clinical data of 105 patients undergoing PLIF between June 2022 and September 2024. Patients were divided into high-dose esketamine group (Group HS, 30 cases), low-dose esketamine group (Group LS, 35 cases) and control group (Group C, 40 cases) based on the preoperative dosages of esketamine. Furthermore, intraoperative sufentanil usage, heart rate (HR) and mean arterial pressure (MAP) were assessed at different times during surgery. Recovery conditions and the length of hospitalization were compared across the three groups. Fatigue levels and psychological status, evaluated using the Christensen fatigue scale, self-rating depression scale (SDS), and self-rating anxiety scale (SAS), were assessed preoperatively and on postoperative days 3 and 5. Pain intensity was assessed using the numeric rating scale (NRS) at 30 min after awakening and on postoperative days 1 and 2. The incidence of POFS and adverse drug reactions (ADRs) was also analyzed among the three groups. **Results**: Compared to T0, MAP and HR scores decreased significantly across all groups from T1 to T3 ($p < 0.05$). From T1–T3, MAP and HR levels were significantly reduced in Group HS than the other groups, while Group LS demonstrated lower levels than Group C ($p < 0.05$). Intraoperative sufentanil usage was also substantially lower in Group HS than the other groups, with Group LS using less than Group C ($p < 0.05$). Upon leaving the recovery room, Group HS had a significantly higher recovery score than the other groups ($p < 0.05$), with Group LS scoring higher than Group C ($p < 0.05$). On postoperative day 3 and 5, Group HS exhibited lower SDS and SAS scores than the other groups ($p < 0.05$), while Group LS exhibited lower scores than Group C ($p < 0.05$). Furthermore, fatigue scores were considerably lower in Group HS compared to the other groups ($p < 0.05$), whereas the difference between Group C and Group LS did not achieve statistical significance ($p > 0.05$). The incidence of POFS in Group HS was 46.67%, significantly lower than in Group LS (88.57%) and Group C (92.50%, $p < 0.05$). On postoperative days 1 and 2, Group HS had lower NRS scores, followed by Group LS, with Group C exhibiting the highest scores ($p < 0.05$). Additionally, there were no significant differences among the three groups in awakening time, extubation time, length of hospitalization, and incidence of ADR ($p > 0.05$). **Conclusion**: Preoperative intravenous esketamine administration effectively prevents POFS in middle-aged and elderly patients undergoing PLIF under general anesthesia in the prone position. An esketamine dose of 0.5 mg/kg shows superior efficacy in reducing postoperative anxiety, depression, and pain levels.

Keywords: esketamine; posterior lumbar interbody fusion; postoperative fatigue syndrome

1. Introduction

Lumbar spine disease is highly prevalent among middle-aged and elderly population [1], with its etiology closely linked to factors such as age, physical condition, lifestyle, and occupational characteristics. Common clinical manifestations include low back pain, radicular pain, and motor dysfunction, all of which can severely affect patient's physical health and quality of life [2]. With the rapid advancement of medical technology, posterior lumbar interbody fusion (PLIF) has gradually become one of the most reliable and effective methods for treating lumbar spine diseases. However, postoperative complications such as surgical trauma, pain, pharmacological side effects, and psychological stress may lead to postoperative fatigue syndrome (POFS). POFS is manifested by a range of symptoms, including exhaustion, muscle weakness, drowsiness, reduced attention, and decreased physical activity. The incidence of POFS ranges from 34% to 87% [3], with about 10% of patients continuing to experience fatigue three months post-surgery, and in some cases, symptoms may persist for up to a year, further influencing daily functioning.

PLIF surgery not only leads to significant postoperative trauma but also requires patients to remain in fixed positions throughout the procedure, which severely disrupts their emotional well-being and sleep quality during

the postoperative recovery period, thus increasing the risk of developing POFS. The onset of POFS negatively affects physical recovery and mental health, creating a vicious cycle that reduces the overall postoperative quality of life [4–6]. Furthermore, it significantly hampers the effective implementation of Enhanced Recovery After Surgery (ERAS) protocols. Previous studies have primarily focused on postoperative rehabilitation training and psychological interventions to prevent and treat POFS, but individual variability often limits the efficacy of these approaches [5,7]. However, the exact mechanisms underlying POFS remain unclear. A study suggests that surgical trauma-induced stress may activate the immune-inflammatory response, which triggers tryptophan metabolism through N-methyl-D-aspartate (NMDA) receptor pathways, leading to the development of POFS [8]. Other evidence indicates that trauma-induced stress increases NMDA receptor expression, potentially disrupting neuronal function and resulting in central fatigue [9].

Esketamine, a right-handed isomer of ketamine and an NMDA receptor antagonist retains the pharmacological properties of ketamine while reducing the incidence of adverse psychological reactions [10]. However, some studies have found that high doses of esketamine may result in cardiovascular instability and fluctuations in mental status [11,12]. In recent years, clinical investigation into POFS has remained largely exploratory and has primarily focused on abdominal surgeries [3,13].

There is a lack of research investigating the prevention and treatment of POFS in middle-aged and elderly patients undergoing lumbar interbody fusion under general anesthesia in the prone position. Based on this gap, exploring the preventive effects of different esketamine doses on POFS in middle-aged and elderly patients could help establish an optimal dosing strategy and provide valuable guidance for clinical application in lumbar fusion surgery.

2. Methods

2.1 Recruitment of Study Participants

This retrospective study included 117 middle-aged and elderly patients scheduled to undergo general anesthesia and posterior lumbar interbody fusion (PLIF) surgery at The First Affiliated Hospital of Bengbu Medical University, China, between June 2022 and September 2024. Patients were divided into three groups: the control group (Group C, 45 patients), the low-dose esketamine group (Group LS, 38 patients), and the high-dose esketamine group (Group HS, 34 patients). In Group C, 5 cases were excluded due to body mass index (BMI) value beyond the range of 18.5–30 kg/m^2, resulting in 40 eligible individuals. In Group LS, 2 cases were excluded because of a history of myocardial infarction within the past 6 months, and 1 case was excluded for requiring blood transfusion during surgery, resulting in 35 included participants. In Group HS, 2 cases were excluded, 2 for BMI beyond the acceptable range and 2 due to more than 600 mL blood loss during surgery, yielding 30 included patients. For specific details, please refer to Fig. 1.

The formula was calculated as follows:

$$n_{ij} = \frac{Z_{1-\alpha/(2t)} + Z^2_{1-\beta} \times \left(\sigma_1^2 + \sigma_2^2 + \sigma_3^2\right)}{\delta_{ij}^2}$$

Where n_{ij} represents the required sample size per group, δ is the permissible error, t represents the number of comparisons, σ is the standard deviation, $\alpha = 0.05$ is the significance range, and β is the Type II error rate corresponding to 90% power.

Preliminary data showed an increase in the Christensen score of 3.02, 2.9, and 2.5 in the corresponding groups, with an overall standard deviation of 0.58. Based on these values, a cohort of 90 individuals (30 cases per group) was calculated to be sufficient to achieve the required statistical power.

The study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Bengbu Medical University (Ethical Human Science NO.320 [2023]). All patients provided informed consent, and the study protocol adhered to the principles outlined in the Declaration of Helsinki issued by the World Medical Association.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria for patient recruitment were as follows: (1) Patients aged $\geq$45 years; (2) Patients undergoing general anesthesia and posterior lumbar interbody fusion surgery; (3) Patients classified as American Society of Anesthesiologists (ASA) physical status I–III [14]; and (4) Those with no preoperative symptoms related to fatigue, anxiety, or depression.

Exclusion criteria included: (1) Long-term use of anesthetic or related drugs before surgery; (2) Hospitalization within the last six months due to cardiovascular diseases such as myocardial infarction or heart failure; (3) Evidence of elevated intracranial pressure or central nervous system damage; (4) History of severe mental illness; (5) Diagnosis of glaucoma or ocular injury; (6) Known allergic to esketamine; (7) Diagnosis of hypertension or hyperthyroidism; (8) Intraoperative blood loss $>$600 mL or need for blood transfusion during the procedure; and (9) BMI beyond the acceptable range of 18.5–30 kg/m^2.

2.3 Preoperative Medication

Upon admission, all patients had intravenous access established through an upper limb vein to facilitate medication and fluid support. Standard monitoring equipment was used to continuously evaluate vital signs, including electrocardiogram (ECG), blood oxygen saturation (SpO2), and blood pressure (BP), to ensure cardiovascular status. Oxygen was supplemented via a nasal cannula at a flow rate of 5 L/min to improve oxygenation.

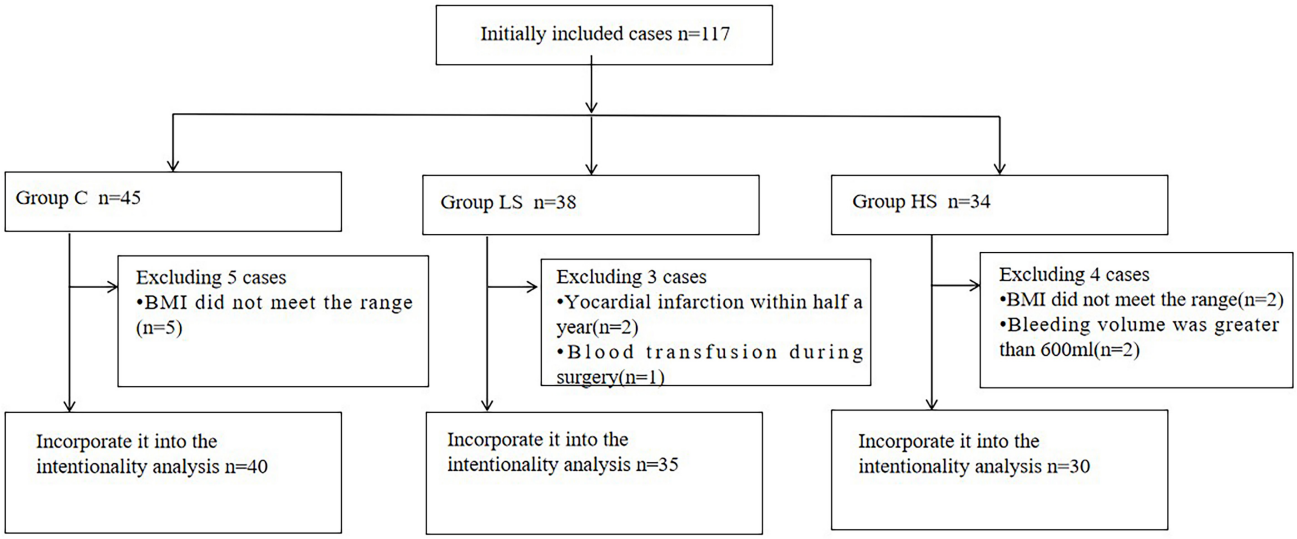

Fig. 1. A flow chart of patient selection. BMI, body mass index; Group HS, high-dose esketamine group; Group LS, low-dose esketamine group; Group C, control group.

In the control group (Group C), no esketamine (Jiangsu HENG RUI Pharmaceutical, China, National Drug Approval No.220816BP) was administered. In the low-dose esketamine group (Group LS), 0.25 mg/kg of esketamine was prepared in 5 mL of saline and administered intravenously 2 minutes before the skin incision. In the high-dose esketamine group (Group HS), 0.5 mg/kg of esketamine, diluted in 5 mL of saline, was administered intravenously 2 minutes before the skin incision [15,16].

2.4 Anesthesia Induction and Maintenance

Anesthesia induction involved sequential intravenous administration of etomidate (Jiangsu Enhua Pharmaceutical, China, National Drug Approval No. TYT24 B01), rocuronium bromide (Jiangsu Hengrui Pharmaceutical, China, National Drug Approval No. 231231XA), and sufentanil citrate (Yichang Renfu Pharmaceutical, China, National Drug Approval No. AB40107221). After adequate muscle relaxation, endotracheal intubation was performed, and mechanical ventilation was initiated employing an anesthesia machine. Initial ventilator settings for tidal volume and respiratory rate were applied and adjusted based on the end-tidal carbon dioxide levels ($EtCO_2$).

Following induction, anesthesia was maintained with continuous intravenous infusion of propofol (Xi'an Libang Pharmaceutical, China, National Drug Approval No. H19990282) and remifentanil (Yichang Renfu Pharmaceutical, China, National Drug Approval No. AC4020061). Additionally, rocuronium bromide was administered as needed to maintain muscle relaxation. The depth of anesthesia was monitored using the Bispectral Index (BIS), with target values maintained between 40 and 60. Hemodynamic stability was supported with norepinephrine (Yuanda Pharmaceutical Co., Ltd., China, National Drug Approval NO. H42021301) and atropine (Runhong Pharmaceutical Co., Ltd., China, National Drug Approval NO. H41020324) as required. After surgery, patients were transferred to the post-anesthesia recovery room with the endotracheal tube in place and were extubated once they regained consciousness.

2.5 Postoperative Pain Management

All patients received patient-controlled analgesia (PCA). The analgesia solution included sufentanil, dezocine (Yangtze River Pharmaceutical, China, National Drug Approval No. H2008032; 4–6 ampoules), and tropisetron (CHIA TAI Tianqing Pharmaceutical, China, National Drug Approval No. 221024), diluted with saline (Jilin Dubang Pharmaceutical, National Drug Approval No. H20083771). The PCA settings were configured with a background infusion rate, bolus dose, lockout interval, and single-dose limit for patient-controlled administration.

2.6 Observational Indicators for Comparative Analysis

(1) Baseline characteristics: Baseline data such as age, gender distribution, ASA classification, BMI, educational level, history of alcohol consumption, smoking status, and underlying medical conditions were recorded and compared among the three groups.

(2) Vital signs at different time points: The anesthesia records identified four time points: T0 (pre-anesthesia), T1 (immediately after starting the procedure), T2 (approximately 20 minutes after beginning surgery), and T3 (end of surgery). Changes in heart rate (HR) and mean arterial pressure (MAP), determined as diastolic pressure plus one-third of the pulse pressure, were recorded at each time point for all three groups and systematically analyzed.

Table 1. Comparison of basic demographic characteristics among the three groups.

Group	Group C (40)	Group LS (35)	Group HS (30)	χ^2/F	*p*-value
Gender				0.320	0.852
Male	15 (37.50)	15 (42.86)	13 (43.33)		
Female	25 (62.50)	20 (57.14)	17 (56.67)		
Mean age (years)	62.88 $\pm$ 8.76	61.69 $\pm$ 8.54	64.00 $\pm$ 9.40	0.552	0.578
BMI (kg/m^2)	25.57 $\pm$ 3.63	24.79 $\pm$ 3.93	26.28 $\pm$ 4.26	1.179	0.312
ASA (%)				1.525	0.822
I	3 (7.50)	2 (5.71)	2 (6.67)		
II	29 (72.50)	27 (77.14)	25 (83.33)		
III	8 (20.00)	6 (17.14)	3 (10.00)		
Educational level (%)				1.277	0.865
Primary school and below	10 (25.00)	9 (25.71)	7 (23.33)		
Junior or senior high school	28 (70.00)	22 (62.86)	21 (70.00)		
College degree or above	2 (5.00)	4 (11.43)	2 (6.67)		
Smoking history (%)	17 (42.50)	15 (42.86)	7 (23.33)	3.432	0.180
Alcohol consumption history (%)	8 (20.00)	12 (34.29)	9 (30.00)	2.025	0.363
Diabetes mellitus (%)	9 (22.50)	8 (22.86)	2 (6.67)	3.703	0.157

Notes: Group C, control group; Group LS, low-dose esketamine group; Group HS, high-dose esketamine group; BMI, body mass index; ASA, American Society of Anesthesiologists.

(3) Recovery metrics: Recovery time, extubation time, intraoperative sufentanil usage, Ramsay sedation scale score [17] at the time of discharge from the recovery room, and the length of hospitalization were all statistically analyzed. Ramsay sedation scores were recorded by trained medical staff, strictly following standardized scoring criteria.

(4) Fatigue evaluation: Fatigue was assessed using the Christensen fatigue scale [18] one day before surgery, and on postoperative day 3 and day 5. Professionally trained medical staff performed all assessments, strictly following standard guidelines. The incidence of POFS was also calculated in all three groups. The Christensen scale ranges from 0 to 10, with a score greater than 2 indicating more severe fatigue. Christensen scoring criteria grade fatigue severity as follows: A score of 1–2 indicates that the patient feels normal, experiences fatigue only after excessive activity, and sleep remains normal; a score of 3–5 indicates that the patient's daily activities are essentially intact, but may experience mild fatigue during higher-intensity activities, which can be relieved with rest, and there is no significant increase in sleep needs; a score of 6–8 shows that the patient can only perform some daily activities, with markedly limited physical strength, feeling more strenuous when walking or climbing stairs, requiring increased sleep time to alleviate fatigue; a score of 9–10 indicates that the patient cannot complete daily activities independently, experiencing extreme exhaustion with significant physical decline, need prolonged sleep to recover strength, and quality of life is significantly diminished. The scale shows good internal consistency, with a Cronbach's α of 0.834.

(5) Pain assessment: Pain intensity was evaluated using the numeric rating scale (NRS) [19] 30 minutes after awakening, and on postoperative days 1 and 2. Scores range from 0 (no pain) to 10 (severe pain). These assessments were performed by trained medical professionals, strictly following standard scoring criteria.

(6) Evaluation of emotional state: Depression and anxiety were assessed using the self-rating depression scale (SDS) [20] and self-rating anxiety scale (SAS) [21] one day before surgery, and on postoperative day 3 and day 5. SDS and SAS scores were classified to determine the severity of depression and anxiety is based on corresponding SDS and SAS scores. All assessments were conducted by professionally trained staff, following standardized criteria.

(7) Adverse drug reactions (ADRs): ADRs occurring within 48 hours after surgery were recorded, and the incidence rates were statistically analyzed across the three groups.

2.7 Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 (IBM, Armonk, NY, USA). For quantitative data, the Shapiro-Wilk test was used to assess normality, and results were expressed as mean $\pm$ standard deviation ($\bar{x} \pm$ s). The one-way ANOVA was applied to compare means among the three groups, followed by the least significant difference (LSD) test for pairwise comparisons. Paired *t*-tests were employed for intra-group comparisons before and after the interventions. Categorical data were presented as frequencies and percentages (%) and were analyzed using the χ^2 test. A p-value < 0.05 indicated statistical significance.

3. Results

3.1 Comparison of Baseline Characteristics Among the Three Groups

There were no significant differences across the three groups regarding age, gender distribution, ASA classifica-

Table 2. Comparison of vital sign changes at different time points among the three groups.

Group (n)	MAP (mmHg)				HR (bpm)			
	T0	T1	T2	T3	T0	T1	T2	T3
Group C (n = 40)	90.75 ± 6.57	87.45 ± 6.46^{a}	80.05 ± 7.31^{ab}	77.75 ± 7.46^{abc}	90.45 ± 7.24	85.55 ± 7.39^{a}	76.30 ± 7.70^{ab}	68.35 ± 7.96^{ab}
Group LS (n = 35)	92.06 ± 5.17	84.37 ± 5.52^{*a}	76.71 ± 5.69^{*ab}	72.86 ± 6.08^{*abc}	90.71 ± 9.83	81.66 ± 7.14^{*a}	71.57 ± 9.60^{*ab}	64.57 ± 7.82^{*abc}
Group HS (n = 30)	91.77 ± 5.45	81.37± 5.03$^{*\#a}$	73.4 ± 4.97$^{*\#ab}$	68.93 ± 4.86$^{*\#abc}$	89.13 ± 6.11	78.00 ± 4.42$^{*\#a}$	66.57 ± 6.28$^{*\#ab}$	60.67 ± 6.73$^{*\#abc}$
F	0.523	9.608	9.990	16.897	0.364	11.366	12.613	8.858
p-value	0.594	<0.001	<0.001	<0.001	0.696	<0.001	<0.001	<0.001

Notes: $^{*}p < 0.05$ vs. Group C; $^{\#}p < 0.05$ vs. Group LS; $^{a}p < 0.05$ vs. T0; $^{b}p < 0.05$ vs. T1; $^{c}p < 0.05$ vs. T2; MAP, mean arterial pressure; HR, heart rate; T0, pre-anesthesia; T1, immediately after starting the procedure; T2, approximately 20 minutes after beginning surgery; T3, end of surgery.

Table 3. Comparison of preoperative recovery and relevant indicators among the three groups.

Group	Awakening time (min)	Extubation time (min)	Intraoperative sufentanil dose (μg)	Ramsay sedation score	Hospitalization length (days)
Group C (n = 40)	9.13 ± 1.50	13.25 ± 1.21	64.05 ± 4.71	1.33 ± 0.47	12.00 ± 3.83
Group LS (n = 35)	9.20 ± 2.06	13.06 ± 1.16	50.96 ± 5.33*	2.37 ± 0.55*	11.86 ± 4.31
Group HS (n = 30)	9.61 ± 2.06	13.43 ± 0.97	34.82 ± 4.74$^{*\#}$	3.17 ± 0.53$^{*\#}$	14.10 ± 6.22
F	0.634	0.895	301.142	112.272	2.215
p-value	0.533	0.412	<0.001	<0.001	0.114

Notes: $^{*}p < 0.05$ vs. Group C; $^{\#}p < 0.05$ vs. Group LS.

tion, BMI, educational level, alcohol consumption history, smoking status and underlying medical conditions ($p > 0.05$). Comparisons across the three groups are presented in Table 1.

3.2 Changes in Vital Signs at Different Time Points During Surgery

Compared with T0, both MAP and HR significantly decreased at time points T1–T3 across all three groups ($p < 0.05$). At T0, there was no significant difference in MAP or HR among the three groups ($p > 0.05$). However, at T1–T3, MAP and HR values in Group HS were significantly lower than those in the other groups, while Group LS also showed significantly lower MAP and HR than Group C ($p < 0.05$, Table 2).

3.3 Comparison of Postoperative Recovery and Related Indicators Among the Three Groups

There were no significant differences among the three groups in postoperative recovery parameters, including awakening time, extubation time, and length of hospitalization ($p > 0.05$). However, intraoperative sufentanil consumption was significantly lower in Group HS (34.82 $\pm$ 4.74 µg) than in Group LS (50.96 $\pm$ 5.33 µg) and Group C (64.05 $\pm$ 4.71 µg), with Group LS indicating substantially lower usage than Group C. Significant differences were observed among the three groups ($p < 0.05$, Table 3). Additionally, Ramsay sedation scores at the time of discharge from the recovery room were significantly higher in Group HS (3.17 $\pm$ 0.53) compared to Group LS (2.37 $\pm$ 0.55) and Group C (1.33 $\pm$ 0.47), with Group LS also scoring higher than Group C. Significant differences were observed among the three groups ($p < 0.05$, Table 3).

3.4 Comparison of Fatigue and POFS Incidence Among the Three Groups

As detailed in Table 4, no significant difference in Christensen fatigue scores was found among the three groups on the day before surgery ($p > 0.05$). However, on postoperative day 3, the Christensen fatigue scores were significantly lower in Group HS (5.40 $\pm$ 1.19) than in Group LS (6.37 $\pm$ 1.19) and Group C (6.68 $\pm$ 1.12) ($p < 0.05$). Similarly, on postoperative day 5 Group HS (4.13 $\pm$ 1.11) demonstrated significantly lower fatigue scores than Group LS (4.63 $\pm$ 0.91) and Group C (4.82 $\pm$ 0.81) ($p < 0.05$).

Furthermore, Christensen fatigue scores increased across all groups and then decreased over time, and statistically significant differences ($p < 0.05$). The incidence of POFS in Group HS was significantly lower (46.67%) than in Group LS (88.57%) and Group C (92.50%), yielding a statistically significant difference among three groups ($p < 0.05$).

3.5 Comparison of Postoperative NRS Scores at Different Time Points Among the Three Groups

There was no significant difference in NRS scores among the three groups 30 min after awakening ($p > 0.05$). However, on postoperative days 1, Group HS showed significantly lower NRS scores (3.33 $\pm$ 0.84) compared to Group LS (4.03 $\pm$ 0.82), and Group LS had significantly lower scores than Group C (4.40 $\pm$ 0.74) (all $p < 0.05$). On postoperative days 2, NRS scores in Group HS (2.23 $\pm$ 0.90) remained significantly lower than those in Group LS (2.83 $\pm$ 0.66) and Group C (3.30 $\pm$ 0.91), with Group LS indicating significantly lower scores than Group C ($p < 0.05$). Pain scores in the three groups decreased progressively over time, and the changes were statistically significant ($p < 0.05$, Table 5).

3.6 Comparison of Emotional State Scores Among the Three Groups

As shown in Table 6, no significant differences in depression and anxiety scores were observed among the three groups on the day before surgery ($p > 0.05$). However, on postoperative days 3 and 5, Group HS demonstrated significantly lower depression and anxiety scores compared to the other groups ($p < 0.05$), and Group LS also exhibited significantly lower scores than Group C ($p < 0.05$). Among all groups, depression and anxiety scores increased postoperatively and then decreased over time, with the differences yielding statistical significance ($p < 0.05$).

3.7 Comparison of Postoperative Complications and ADR Incidence Among the Three Groups

All patients were followed up postoperatively, and ADRs occurring within 48 hours post-surgery were recorded. In Group C, 2 patients experienced nausea and vomiting, resulting in an ADR incidence of 5.00%. In Group LS, 2 patients reported nausea, with an ADR incidence of 5.71%. In Group HS, 1 patient experienced drowsiness, indicating an incidence of 3.33%. However, no significant difference in ADR incidence was observed among the three groups ($p > 0.05$, Table 7).

4. Discussion

The incidence of lumbar degenerative diseases in China has been increasing in recent years. With improvements in living standards and advances in medical technology, an increasing number of people are opting for surgical treatments to enhance their quality of life. Despite successful surgeries, many patients still report postoperative complications, including psychological conditions such as depression and even suicidal thoughts. Consequently, since the early 21st century, China's healthcare system has gradually shifted towards the biopsychosocial model of care.

Lumbar spine surgery is associated with significant surgical trauma, and the need for patients to maintain a fixed position during and after surgery leads to physical stiffness

Table 4. Comparison of christensen fatigue scores and POFS incidence at different time points among the three groups.

Group	Christensen fatigue score			POFS incidence (%)
	Preoperative day 1	Postoperative day 3	Postoperative day 5	
Group C (n = 40)	1.78 ± 0.70	6.68 ± 1.12^{a}	4.82 ± 0.81^{ab}	37 (92.50)
Group LS (n = 35)	1.77 ± 0.73	6.37 ± 1.19^{a}	4.63 ± 0.91^{ab}	31 (88.57)
Group HS (n = 30)	1.63 ± 0.72	5.40 ± 1.19$^{*\#a}$	4.13 ± 1.11$^{*\#ab}$	14 (46.67)$^{*\#}$
F/χ^2	0.411	10.796	4.811	24.422
p-value	0.664	<0.001	0.010	<0.001

Notes: $^{*}p < 0.05$ vs. Group C; $^{\#}p < 0.05$ vs. Group LS; $^{a}p < 0.05$ vs. Preoperative day 1; $^{b}p < 0.05$ vs. Postoperative day 3; POFS, postoperative fatigue syndrome.

Table 5. Comparison of postoperative NRS scores at different time points among the three groups.

Group	30 min after awaking	Postoperative day 1	Postoperative day 2
Group C (n = 40)	5.38 ± 0.67	4.40 ± 0.74^{a}	3.30 ± 0.91^{ab}
Group LS (n = 35)	5.40 ± 0.60	4.03 ± 0.82^{*a}	2.83 ± 0.66^{*ab}
Group HS (n = 30)	5.37 ± 0.49	3.33 ± 0.84$^{*\#a}$	2.23 ± 0.90$^{*\#ab}$
F	0.028	15.382	14.066
p-value	0.972	<0.001	<0.001

Notes: $^{*}p < 0.05$ vs. Group C; $^{\#}p < 0.05$ vs. Group LS; $^{a}p < 0.05$ vs. 30 min after awaking; $^{b}p < 0.05$ vs. Postoperative day 1.

and discomfort, especially among the middle-aged and elderly. These factors often exacerbate postoperative fatigue, which can impact long term functional recovery and overall quality of life. Postoperative fatigue syndrome (POFS) is a common complication after lumbar spine surgery, with an incidence rate ranging from 30% to 70%, severely affecting postoperative recovery and psychological health. Current clinical methods for preventing and treating POFS include reducing surgical trauma and stress response, improving nutritional support, and providing psychological care; however, these approaches have yielded limited success. Therefore, investigating new and more effective intervention strategies is crucial to improving prognosis in middle-aged and elderly patients undergoing lumbar spine surgery in the prone position.

Esketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, works by blocking excessive neuronal excitation at NMDA receptor sites, thereby alleviating pain and discomfort associated with surgery. Research evidence has indicated that perioperative use of esketamine can promote the recovery of physical function, prevent postoperative loss in activity levels, and reduce postoperative fatigue [3]. Lin *et al.* [22] reported that esketamine effectively prevents POFS, potentially through a mechanism involving immune system activation and inhibition of inflammatory activities. However, the optimal dosage of esketamine for POFS prevention has not yet been established in current clinical guidelines. In practice, dosing is often based on clinical experience, leading to significant debate regarding its appropriate application. This study, for the first time, systematically assesses the effects of different postoperative doses of esketamine in middle-aged and elderly patients undergoing general anesthesia for lumbar interbody fusion surgery.

The results of this study indicate that vital sign fluctuations occurred across different intraoperative time points in all three groups. Notably, compared to Group C and Group LS, Group HS exhibited the most significant fluctuations in MAP and HR. This may be due to the inhibitory effect of high-dose esketamine on sympathetic nervous activity, leading to decreased HR and BP, thereby alleviating MAP. Furthermore, high-dose esketamine may reduce cardiac contractility and decrease cardiac output, further contributing to the reduction in MAP. Moreover, patients with reduced cardiac adaptability may be more vulnerable to these effects.

Intraoperative sufentanil consumption was significantly lower in Groups HS and LS compared to Group C, with Group HS exhibiting the lowest usage. These observations suggest that esketamine possesses analgesic effects that reduce the need for opioids. Furthermore, Ramsay sedation scores recorded at the time of discharge from the recovery room were significantly higher in Group HS, followed by Group LS, and lowest in Group C. These findings suggest that high-dose esketamine provides better sedation and anesthetic effects compared to lower doses.

Postoperative pain evaluation revealed substantially lower NRS scores in Group HS on postoperative days 1 and 2, indicating its enhanced ability to alleviate postoperative pain. This effect may be due to esketamines's NMDA receptor antagonism, which inhibits excessive neural excitation and disrupts pain signal transmission in the spinal cord

Table 6. Comparison of SDS and SAS scores at different time points among the three groups.

Group	SDS score			SAS score		
	Preoperative day 1	Postoperative day 3	Postoperative day 5	Preoperative day 1	Postoperative day 3	Postoperative day 5
Group C (n = 40)	46.35 ± 3.57	56.90 ± 4.05^{a}	49.45 ± 3.71^{ab}	48.35 ± 3.81	55.10 ± 2.94^{a}	51.33 ± 2.87^{ab}
Group LS (n = 35)	47.29 ± 3.02	55.11 ± 3.24^{*a}	44.63 ± 3.13^{*ab}	48.31 ± 3.76	53.60 ± 2.30^{*a}	47.17 ± 2.47^{*ab}
Group HS (n = 30)	47.23 ± 2.92	53.00 ± 3.06$^{*\#a}$	42.53 ± 2.43$^{*\#ab}$	48.43 ± 3.89	50.53 ± 3.33$^{*\#a}$	45.33 ± 2.47$^{*\#ab}$
F	0.998	10.490	44.183	0.008	22.016	48.805
p-value	0.372	<0.001	<0.001	0.992	<0.001	<0.001

Notes: $^{*}p < 0.05$ vs. Group C; $^{\#}p < 0.05$ vs. Group LS; $^{a}p < 0.05$ vs. Preoperative day 1; $^{b}p < 0.05$ vs. Postoperative day 3; SDS, self-rating depression scale; SAS, self-rating anxiety scale.

Table 7. Comparison of ADR rates among the three groups.

Group	Group C (n = 40)	Group LS (n = 35)	Group HS (n = 30)
Number of ADR	2	2	1
The incidence of ADR (%)	5.00	5.71	3.33
p-value		0.895	
χ^2		0.221	

Notes: ADR, adverse drug reaction.

and brain. Additionally, it may regulate other neurotransmitters and enhance the release of endogenous opioids, further contributing to its analgesic effects [23].

Regarding psychological function assessments, both SDS and SAS scores were substantially lower in Groups HS and LS compared to Group C, which is consistent with previous studies [24,25]. On postoperative day 5, the incidence of POFS in Group HS was significantly lower than in Group C. Moreover, fatigue scores on postoperative days 3 and 5 were significantly lower in Group HS compared to the other groups. While Group LS exhibited a slight improvement in fatigue scores than Group C, the difference was not statistically significant. These results suggest that high-dose esketamine is more effective in alleviating postoperative fatigue and promoting recovery, potentially through its dose-dependent effects on mood modulation and fatigue alleviation. Future studies should explore the optimal dosage range to maximize therapeutic effects while minimizing postoperative adverse reactions.

The incidence of ADRs did not differ substantially among the three groups, indicating that preoperative intravenous administration of esketamine does not increase safety risks for patients undergoing lumbar spine surgery in the prone position. The safety of high-dose esketamine still meets clinical requirements.

This study primarily investigates differences among three groups of patients at specific time points, aiming to assess the varying effect of different esketamine dosages on POFS. Therefore, one-way ANOVA combined with paired *t*-test was employed to analyze both between-group and within-group differences at individual time points. Currently, the postoperative follow-up period is relatively short, and no significant temporal trends have been observed. Interaction effects across multiple time points have not yet been explored. Future research will utilize repeated measures ANOVA to further examine and validate the dynamic changes in drug effects over time.

Despite some promising findings, we acknowledge certain limitations in this study. Firstly, while our follow-up results at 5 days post-surgery showed that a single intravenous dose of 0.5 mg/kg esketamine effectively reduced postoperative fatigue scores, long-term follow-up data were not recorded. Although we speculate that the short-term advantages of esketamine may have positive impacts on long-term recovery, further research is needed to confirm this assumption. Secondly, this study was conducted in a single center with a relatively small sample size, which may limit its generalizability. Future investigations involving multicenter trials with larger sample sizes are warranted to further validate these results. Finally, this study only included patients undergoing elective lumbar interbody fusion surgery who had good baseline health conditions and were receiving general anesthesia for the first time. Consequently, whether esketamine exerts similar beneficial impacts in broader patient cohorts outside these inclusion criteria remains to be explored through further research.

5. Conclusion

In conclusion, preoperative intravenous esketamine effectively prevents POFS in middle-aged and elderly patients undergoing lumbar spine surgery in the prone position. It helps alleviate postoperative psychological distress, provides rapid pain relief, and meets clinical safety requirements. Compared to the 0.25 mg/kg dose, a 0.5 mg/kg dose shows better efficacy in preventing POFS and contributes to Enhanced Recovery After Surgery. These results underscore the potential of esketamine as a promising adjunct in preoperative care and warrant further investigation.

Key Points

- Preoperative intravenous esketamine effectively prevents POFS in middle-aged and elderly patients undergoing lumbar spine surgery in the prone position.
- Preoperative intravenous esketamine alleviates postoperative psychological distress, offers rapid pain relief, and meets clinical safety standards.
- Compared to the 0.25 mg/kg dose, a 0.5 mg/kg dose is more effective in preventing POFS.
- A 0.5 mg/kg dose contributes to the implementation of Enhanced Recovery After Surgery.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

WQL conceived and designed the study. WQL, HCC and QML collected the patients'cases. WQL, HCC and HCH analyzed the data. WQL, HCC, QML and HCH drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study has been approved by the Medical Ethics Committee of The Frist Affiliated Hospital of Bengbu Medical University (Ethical Human Science NO.320 [2023]) and strictly adheres to the principles outlined in the Declaration of Helsinki. The patients included in the study have signed the informed consent form.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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