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Original Article

Esketamine has promising anti-inflammatory effects in orthopedic surgery and plays a protective role in postoperative cognitive function and pain management

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Abstract: Objective: To investigate the effects of subanesthetic doses of esketamine on serum inflammatory cytokine levels and its impact on postoperative cognition and pain in patients undergoing elective orthopedic surgery. Methods: From November 2023 to March 2024, patients scheduled for elective orthopedic surgery were randomly divided into an observation group or a control group, with 100 patients in each group (ChiCTR2300079156). The observation group received an intravenous injection of 0.25 mg/kg esketamine before the induction of general anesthesia, while the control group was administered an equivalent volume of normal saline. Postoperative measurements included serum levels of interleukin-6 (IL-6), interleukin-1 (IL-1), and interleukin-10 (IL-10), as well as immunoglobulin levels (IgM and IgG), complete blood count (including white blood cell count, hemoglobin, and platelet count), intraoperative blood loss, cognitive function scores (assessed using the Mini-Mental State Examination [MMSE]), postoperative pain scores, and the incidence of adverse reactions (including nausea, vomiting, headache, dizziness, hallucinations, agitation, allergic reactions, and cardiovascular and respiratory responses). Results: Postoperatively, serum levels of IL-6 and IL-1 in the observation group were significantly lower than those in the control group ($P<0.05$), while IL-10 levels were significantly higher ($P<0.05$). The control group showed a significant decrease in immunoglobulin levels (IgM and IgG) after surgery, whereas the observation group exhibited higher postoperative immunoglobulin levels compared to control group. In terms of complete blood count, the observation group had significantly better white blood cell and platelet counts compared to the control group ($P<0.05$), with no significant difference in hemoglobin levels. Intraoperative blood loss was significantly lower in the observation group ($P<0.05$). Cognitive function, as measured by the MMSE scores, was significantly better in the observation group compared to the control group at 6 and 24 hours postoperatively ($P<0.05$). Additionally, the observation group had significantly lower pain scores at 6 and 24 hours postoperatively and a lower incidence of adverse reactions. Conclusion: Subanesthetic doses of esketamine in elective orthopedic surgery can effectively reduce postoperative inflammatory cytokine levels, improve immunoglobulin levels, reduce intraoperative blood loss, protect postoperative cognitive function, and significantly decrease the incidence of postoperative pain and adverse reactions. These findings suggest that subanesthetic dosing of esketamine has a high level of safety and efficacy in this clinical setting.

Keywords: Esketamine, inflammatory cytokines, orthopedic surgery, cognitive function, adverse reactions, complete blood count

Introduction

Elective orthopedic surgery plays a crucial role in the field of surgery, with postoperative recovery and prognosis directly impacting the patient's quality of life. However, the surgical procedure itself is inherently traumatic and often triggers the activation of the body's inflammatory response. This inflammatory reaction not only increases the risk of postoperative complications but also negatively affects immune function and cognitive abilities. Recent studies have highlighted the importance of controlling postoperative inflammation to improve patient outcomes [1]. Esketamine, a commonly used anesthetic with both analgesic and anti-inflam-

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matory properties, has garnered increasing attention for its potential benefits when administered at subanesthetic doses. Previous studies have demonstrated that low dose esketamine can modulate immune responses and reduce inflammatory cytokine levels, thereby decreasing the incidence of postoperative complications [2, 3]. However, there is a lack of systematic research on the effects of subanesthetic doses of esketamine on serum inflammatory cytokine levels and other related physiological indicators in patients undergoing elective orthopedic surgery [4, 5]. Therefore, this study aims to investigate the impact of subanesthetic doses of esketamine on postoperative serum inflammatory cytokine levels, immunoglobulin levels, complete blood count parameters, intraoperative blood loss, cognitive function, and the incidence of adverse reactions in patients undergoing elective orthopedic surgery.

Materials and methods

General information

A prospective study design was employed, enrolling 200 patients scheduled for elective orthopedic surgery at Xi'an International Medical Center Hospital from November 2023 to March 2024. Patients were randomly assigned to either the observation group (esketamine) or the control group (placebo) using a random number table, with 100 patients in each group (clinical trial registration number: ChiCTR2300079156). This study was approved by the Medical Ethics Committee of Xi'an International Medical Center Hospital. All patients in the study signed informed consent forms.

Inclusion Criteria: (1) Patients undergoing elective orthopedic surgery under general anesthesia; (2) Age between 18 and 89 years, regardless of gender; (3) American Society of Anesthesiologists (ASA) physical status classification of I-III.

Exclusion Criteria: (1) Patients with cardiac, pulmonary, hepatic, or renal insufficiency; (2) Patients with hematological disorders; (3) History of medication use within 1 month prior to surgery, including opioid analgesics, nonsteroidal anti-inflammatory drugs, antibiotics, or antidepressants; (4) History of alcohol abuse; (5) Patients with psychiatric disorders; (6) Patients with endocrine-related diseases such as thyroid disease, diabetes, or hypothalamic-pituitary-adrenal axis disorders; (7) Use of sedatives, antiemetics, or antipruritic medications within 24 hours before surgery; (8) Pregnant or lactating women; (9) Individuals unable to understand verbal instructions; (10) Any other factors that may influence the outcome of the trial.

Study methods

Preoperative preparation: Intravenous access was established, and blood oxygen saturation (SpO_2), non-invasive blood pressure (NIBP), and electrocardiography (ECG) were continuously monitored.

Anesthesia induction: In the observation group, 0.25 mg/kg of esketamine was administered intravenously before the induction of general anesthesia. Anesthesia was subsequently induced with 0.3 mg/kg etomidate, 0.6 mg/kg rocuronium, and 0.5 μg/kg sufentanil, followed by the administration of propofol. In the control group, an equivalent volume of 0.9% sodium chloride solution (placebo) was administered intravenously before the induction of general anesthesia, followed by the same anesthesia induction protocol (0.3 mg/kg etomidate, 0.6 mg/kg rocuronium, and 0.5 μg/kg sufentanil), with propofol subsequently administered.

Anesthesia maintenance: Anesthesia was maintained with propofol and remifentanil. The anesthesiologist adjusted the infusion rates of both propofol and remifentanil based on the patient's vital signs throughout the surgery.

Observation indicators

Primary observation indicators: (1) Comparison of serum inflammatory cytokine levels: Serum levels of interleukin-6 (IL-6), interleukin-1 (IL-1), and interleukin-10 (IL-10) were measured using enzyme-linked immunosorbent assay (ELISA). The assay kits were purchased from R&D Systems (IL-6 kit number: JL20268, IL-1 kit number: DEC05433, IL-10 kit number: JK-EA00031), and all procedures were performed in strict accordance with the manufacturer's instructions. (2) Measurement of immunoglobulin levels: Serum levels of immunoglobulin G (IgG) and immunoglobulin M (IgM) were measured using immunoturbidimetry. The assay kits were obtained from Roche (IgG kit number: IGG0030,

IgM kit number: YM-1207B), and the procedures were carried out strictly following the manufacturer's protocol. (3) Cognitive function assessment: Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) scoring system. The score ranges from 0 to 30, with lower scores indicating poorer cognitive function. Scores >27: Total score of normal cognitive function; Scores 23-26: Total score of mild cognitive impairment; Scores 17-22: moderate cognitive impairment; Scores ≤16: severe cognitive impairment.

Secondary observation indicators: (1) Complete blood count parameters: Complete blood count parameters, including white blood cell count, hemoglobin, and platelet count, were measured using an automated hematology analyzer (Beckman Coulter). (2) Adverse reactions: The occurrence of adverse reactions, including nausea, vomiting, headache, dizziness, hallucinations, agitation, allergic reactions, and cardiovascular and respiratory responses, was monitored and recorded in both groups. (3) Intraoperative blood loss: The volume of intraoperative blood loss was recorded for both groups. (4) Postoperative pain assessment: Postoperative pain levels were assessed using the Visual Analogue Scale (VAS), with pain scores recorded at 6 and 24 hours postoperatively and compared between the two groups. The score ranges from 0 to 10, with a higher score indicating more severe pain. The scoring criteria are as follows: 0: no pain; Scores 1-3: mild pain (pain is lightly perceived and usually does not interfere with daily activities); Scores 4-6: moderate pain (pain is strong and affects daily activities, but can be tolerated); Scores 7-9: severe pain (pain is severe, significantly affects daily activities, and requires medical intervention); Score 10: Severe pain (unbearable pain that severely interferes with daily life and requires emergency intervention).

Statistical analysis

SPSS 20.0 software was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and the t-test was used for comparisons between groups. Paired t-tests were used to compare pre- and post-treatment values within the same group. Count data were expressed as quantity and percentage (n, %), and differences between groups were assessed by chi-square test (χ^2). A *p*-value of <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between the two groups

There were no statistically significant differences between the two groups in terms of age, gender, time from fracture to hospital admission, reason for surgery (including fracture repair, joint replacement, spinal surgery, ligament repair and reconstruction, soft tissue repair, orthopedic surgery, tumor resection, and infection control), or ASA classification (all P>0.05), indicating that the groups were comparable (**Table 1**).

Comparison of serum inflammatory cytokine levels between the two groups

Postoperatively, serum levels of inflammatory cytokines (IL-6, IL-1, IL-10) increased in both groups compared to preoperative levels. However, the observation group had significantly lower levels of IL-6 and IL-1, and significantly higher levels of IL-10, compared to the control group (P<0.05) (**Table 2**).

Comparison of immunoglobulin levels between the two groups

Postoperatively, the immunoglobulin levels (IgG and IgM) significantly decreased in the control group, whereas the observation group exhibited significantly higher levels of both IgG and IgM compared to the control group (P<0.05) (**Figure 1**).

Comparison of intraoperative blood loss between the two groups

Intraoperative blood loss was significantly lower in the observation group compared to the control group (P<0.05) (**Figure 2**).

Comparison of complete blood count parameters between the two groups

Postoperatively, the white blood cell count was significantly elevated in both groups compared to preoperative levels (P<0.05). However, the white blood cell count in the observation group was significantly lower than in the control group

Table 1. Comparison of baseline characteristics between the two groups

Variables	Observation group (n=100)	Control group (n=100)	Statistical Values	P
Age (years)	55.61±18.34	54.81±19.12	t=0.302	0.763
Gender			χ^2=0.080	0.777
Male	52	50		
Female	48	50		
Time from Fracture to Admission (days)	3.21±1.52	3.30±1.45	t=0.428	0.669
Reason for Surgery			χ^2=8.177	0.317
Fracture Repair	14	18		
Joint Replacement	14	12		
Spinal Surgery	5	10		
Ligament Repair and Reconstruction	10	16		
Soft Tissue Repair	16	10		
Orthopedic Surgery	14	9		
Tumor Resection	11	15		
Infection Control	16	10		
ASA Classification			χ^2=0.105	0.949
I	30	32		
II	50	48		
III	20	20		

Table 2. Comparison of serum inflammatory cytokine levels between the two groups ($\bar{x}$±s)

Group	IL-6		IL-1		IL-10	
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
Observation group (n=100)	16.43±2.72	36.61±4.33$^{*,\#}$	28.70±3.32	47.51±5.43$^{*,\#}$	41.61±17.78	149.62±42.54$^{*,\#}$
Control group (n=100)	16.31±2.92	50.31±6.48$^{\#}$	28.52±2.53	58.82±6.24$^{\#}$	45.26±16.82	76.32±22.33$^{\#}$
t	0.301	-17.579	0.431	-13.673	-1.491	15.257
P	0.764	<0.001	0.667	<0.001	0.137	<0.001

Note: Compared to pre-operative levels, $^{\#}$P<0.05; compared to the control group, *P<0.05.

(P<0.05). There was no statistically significant difference in hemoglobin levels before and after surgery in either group. Postoperatively, the platelet count in the control group was significantly lower than preoperative levels (P< 0.05), whereas the platelet count in the observation group was significantly higher than in the control group (P<0.05) (**Table 3**).

Comparison of MMSE cognitive function scores between the two groups

There was no statistically significant difference in MMSE scores between the two groups preoperatively (P>0.05). However, the observation group had significantly higher MMSE scores at 6 and 24 hours postoperatively compared to the control group (P<0.05) (**Figure 3**).

Comparison of postoperative pain scores between the two groups

The observation group exhibited significantly lower pain VAS scores at 6 and 24 hours postoperatively compared to the control group (P<0.05) (**Table 4**).

Comparison of incidence of adverse reactions between the two groups

The incidence of adverse reactions, including nausea, vomiting, headache, dizziness, hallucinations, agitation, allergic reactions, and cardiovascular and respiratory responses, was significantly lower in the observation group compared to the control group (P<0.05) (**Table 5**).

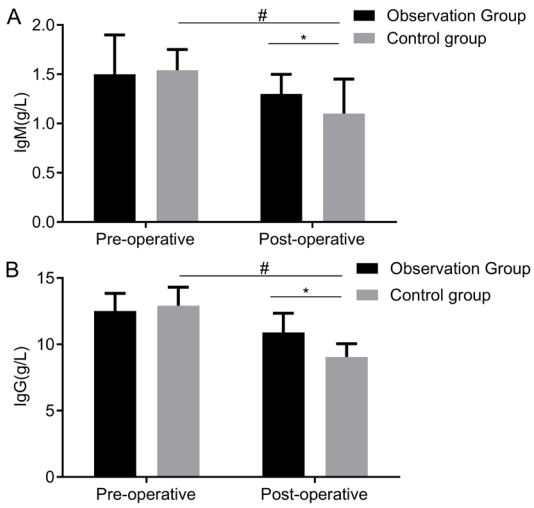

Figure 1. Comparison of immunoglobulin levels between the two groups. A: Comparison of IgM levels between the two groups. B: Comparison of IgG levels between the two groups. Note: Compared to preoperative levels, #P<0.05; Compared to the control group, *P<0.05.

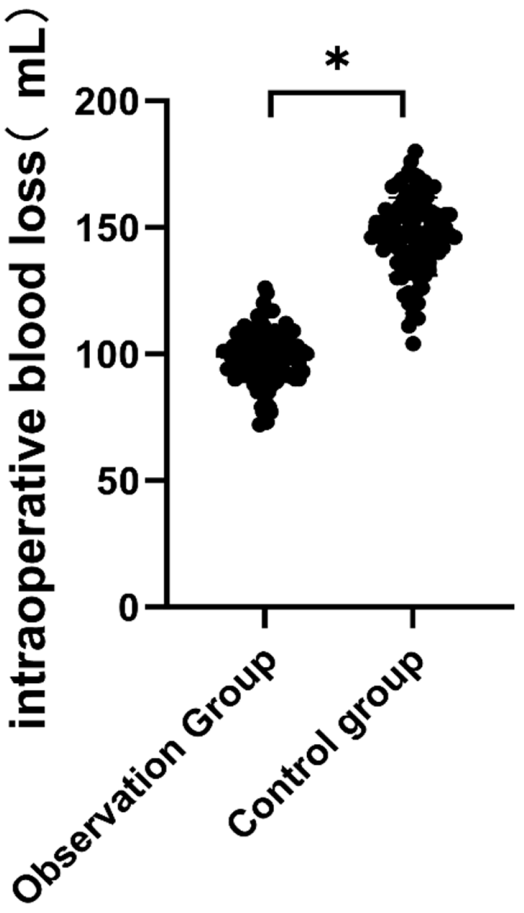

Figure 2. Comparison of intraoperative blood loss between the two groups. Note: Compared to the control group, *P<0.05.

Discussion

This study found that low-dose esketamine significantly reduced postoperative serum levels of IL-6, IL-1, and IL-10 compared to the control group. These results are consistent with findings from previous studies [6-8]. Specifically, Gao et al., and Tang et al., demonstrated that esketamine could significantly reduce inflammatory cytokines, including IL-6 and IL-1 [6, 7]. In a mouse model of acute lung injury, Yang et al. found that esketamine significantly reduced the expression of IL-6 and IL-1 while increasing IL-10 levels [8]. The mechanisms underlying the reduction of postoperative inflammatory cytokine levels and immune modulation by esketamine involve two primary processes. First, as an N-methyl-D-aspartate receptor (NMDAR) antagonist, esketamine inhibits NMDAR activation, thereby reducing calcium ion influx into neurons and immune cells. This inhibition subsequently attenuates the production and release of inflammatory mediators [9]. Second, esketamine can suppress the NF-κB signaling pathway, a key regulator of the inflammatory response. By inhibiting NF-κB activation, esketamine decreases the release of IL-6 and IL-1 [10]. Additionally, esketamine modulates the proportion of T cell subsets, including the Th17/Treg ratio, by suppressing the activity of pro-inflammatory Th17 cells and promoting the proliferation and function of anti-inflammatory Treg cells. This modulation results in reduced levels of IL-6 and IL-1, while increasing IL-10 levels [11]. Liu et al. also highlighted that esketamine effectively reduces the inflammatory response by decreasing the expression of TNF-α [12]. These combined mechanisms contribute to the significant anti-inflammatory effects of esketamine in postoperative management.

This study also observed that postoperative immunoglobulin levels (IgM and IgG) in the control group significantly decreased compared to preoperative levels, whereas immunoglobulin levels in the observation group were significantly higher than those in the control group. This suggests that subanesthetic doses of esketamine may have a positive effect on immune function. Immunoglobulins play a critical role in the body's immune defense, and changes in their levels directly reflect the immune status of the individual [13, 14]. Surgical stress typically suppresses the immune system, leading to a

Table 3. Comparison of routine blood indexes between the two groups ($\bar{x}\pm s$)

Group	Platelet Count ($\times10^9$/L)		Hemoglobin Levels (g/L)		White Blood Cell Count ($\times10^9$/L)	
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
Observation group (n=100)	266.61±62.71	221.62±48.82	126.71±9.47	127.30±10.64	8.80±2.34	11.68±1.70
Control group (n=100)	252.60±62.63	197.33±46.23*,#	125.42±7.31	129.82±10.31*,#	9.35±2.83	14.51±1.45*,#
t	1.581	3.616	1.078	1.701	1.498	12.666
P	0.116	<0.001	0.282	0.091	0.136	<0.001

Note: Compared to pre-operative levels, #P<0.05; Compared to the control group, *P<0.05.

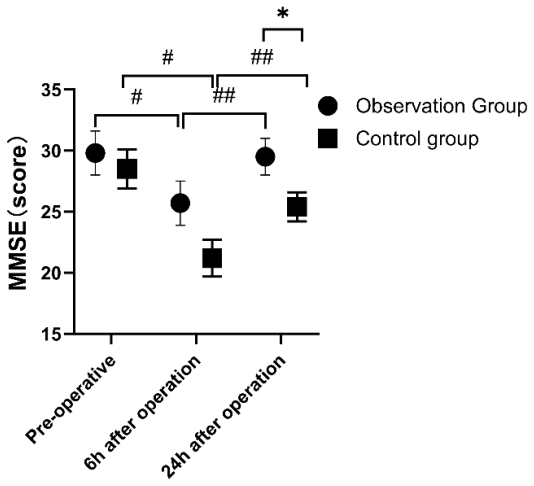

Figure 3. Comparison of MMSE cognitive function scores between the two groups. Note: MMSE: Mini-Mental State Examination; Compared to pre-operative levels, #P<0.05; compared to 6 h after operation, ##P<0.05; compared to the control group, *P<0.05.

decline in immunoglobulin levels, which explains the significant decrease in immunoglobulin levels observed in the control group postoperatively. The maintenance of immunoglobulin levels in the observation group may be related to the immunomodulatory effects of esketamine. Other studies have also indicated that esketamine possesses immunomodulatory properties. For instance, Chen et al. found that low doses of esketamine can alleviate surgery-induced immunosuppression and help maintain immunoglobulin levels [15]. Similarly, Chen et al. demonstrated that subanesthetic doses of esketamine not only inhibit the release of inflammatory cytokines but also increase IgG and IgM levels [16]. These findings align with the results of this study and further support the immunoprotective effects of esketamine. The underlying mechanism may involve esketamine's inhibition of NMDA receptors, leading to a reduction in the release of inflammatory cytokines such as IL-6 and IL-1. This reduction in cytokines may alleviate suppression of the immune system, thereby helping to maintain normal immunoglobulin levels.

This study further investigated the impact of esketamine on complete blood count parameters. Postoperatively, white blood cell counts were significantly elevated compared to preoperative levels; however, the observation group showed significantly lower white blood cell counts than the control group. Smith et al. have demonstrated that postoperative inflammatory responses can lead to a significant increase in white blood cell counts, and that esketamine can effectively attenuate this increase [17]. This effect is likely attributed to esketamine's ability to inhibit NMDA receptors and the NF-κB signaling pathway, which reduces the release of pro-inflammatory cytokines, mitigates the postoperative inflammatory response, and ultimately lowers white blood cell counts. Additionally, the observation group had significantly higher platelet counts after surgery compared to the control group, which is consistent with the findings of Wang et al., who reported that postoperative administration of esketamine helps maintain platelet counts and reduces the risk of postoperative bleeding [18]. Esketamine achieves this by reducing the release of inflammatory mediators, thereby minimizing platelet consumption while promoting platelet production and maintaining their function. This study also found no statistically significant differences in hemoglobin levels between the two groups before and after surgery. This result is in line with the findings of Chen et al., who reported that surgery itself does not significantly affect hemoglobin levels, particularly in the absence of substantial blood loss [19]. Since the types of surgeries and patient conditions in

Table 4. Comparison of postoperative pain scores between the two groups ($\bar{x}\pm s$)

Group	Pain Scores for Postoperative 6 Hours	Pain Scores for Postoperative 24 Hours
Observation group (n=100)	3.2±0.8	2.5±0.6
Control group (n=100)	5.1±1.2	4.3±1.0
t	-13.174	-15.435
P	<0.001	<0.001

Table 5. Comparison of adverse reactions between the two groups

Group	Control group (n=100)	Observation group (n=100)	X^2	p
Nausea	4	1	6.452	0.011
Vomiting	2	1		
Headache	3	1		
Dizziness	5	2		
Hallucination	1	0		
Agitation	2	1		
Allergic Reaction	1	0		
Cardiovascular Reaction	2	2		
Respiratory Reaction	2	1		
Total	22	9		

this study did not lead to significant blood loss, changes in hemoglobin levels were minimal. Furthermore, the observation group experienced significantly lower intraoperative blood loss compared to the control group, suggesting that esketamine also exerts an effect in reducing intraoperative bleeding.

The study further evaluated the effects of esketamine on cognitive function, with findings consistent with those of Nikayin S et al. and Qiu D et al., both of whom demonstrated that esketamine has a positive impact on postoperative cognitive function [20, 21]. Research has shown that postoperative oxidative stress is a major contributor to cognitive dysfunction [22]. Esketamine, with its antioxidant properties, can mitigate oxidative stress-induced neuronal damage. By reducing the production of free radicals and enhancing the activity of antioxidant enzymes, esketamine helps protect the brain from oxidative damage. As an NMDA receptor antagonist, esketamine can also protect nerve cells from excitotoxicity mediated by NMDA receptors [23, 24]. This mechanism helps reduce postoperative neuronal injury and cell death, thereby improving cognitive function. VAS pain scores further indicated that patients in the observation group had significantly lower pain levels at 6 and 24 hours postoperatively compared to the control group, further supporting the effectiveness of esketamine in postoperative analgesia. This analgesic effect of esketamine is likely due to its ability to inhibit the release of postoperative inflammatory cytokines such as IL-6 and IL-1, thereby reducing inflammation-mediated pain responses. Additionally, the elevated levels of IL-10 observed in the observation group may have contributed to both anti-inflammatory and analgesic effects, further alleviating postoperative pain. The incidence of adverse reactions, including nausea, vomiting, headache, dizziness, hallucinations, agitation, allergic reactions, as well as cardiovascular and respiratory responses, was significantly lower in the observation group compared to the control group. These findings suggest that low dose esketamine is relatively safe, with a low incidence of adverse effects. This favorable safety profile is likely due to esketamine's ability to exert its analgesic and anti-inflammatory effects at low doses.

Despite the finding that subanesthetic doses of esketamine exhibit significant anti-inflammatory effects and improve postoperative cognitive function in elective orthopedic surgery, this study has several limitations. First, the relatively small sample size may limit the generalizability of the results. Future studies should aim to increase the sample size to enhance the statistical power and reliability of the findings. Second, as a single-center study, the results may be influenced by the specific patient population and clinical conditions at the hospital, limiting their broader applicability. Multicenter studies are needed to provide more robust and generalizable data. Additionally, the study had a short follow-up period, primarily focusing on short-term postoperative effects, lacking data on long-term outcomes. Future studies should

extend the follow-up period to assess the sustained impact of esketamine on patient outcomes. Furthermore, the reporting of adverse reactions in this study was not exhaustive, as it did not systematically evaluate all potential adverse effects. Future research should involve comprehensive monitoring and detailed reporting of adverse reactions to better assess the safety profile of esketamine. Lastly, while this study focused primarily on clinical outcomes, it did not delve deeply into the underlying molecular mechanisms of esketamine's effects. To deepen our understanding of its anti-inflammatory and cognitive-enhancing properties, future studies should incorporate basic experimental research to further elucidate the specific molecular pathways involved. By addressing these limitations, future research can provide a more comprehensive evaluation of the application of subanesthetic doses of esketamine in elective orthopedic surgery, thereby strengthening the evidence base to support its clinical application.

In conclusion, subanesthetic doses of esketamine in elective orthopedic surgery effectively reduce postoperative inflammatory cytokine levels, improve immunoglobulin concentrations, decrease intraoperative blood loss, protect postoperative cognitive function, significantly lower the incidence of postoperative pain, and reduce the occurrence of adverse reactions, demonstrating high efficacy and a favorable safety profile.

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Disclosure of conflict of interest

None.

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