

Effects of Intravenous Esketamine or Magnesium Sulfate on Early Postoperative Negative Emotions and Pain in Patients Undergoing Endoscopic Sinus Surgery: A Randomized Controlled Trial

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Background: N-methyl-D-aspartate (NMDA) receptor antagonists are crucial for managing perioperative pain and psychological distress. Both esketamine and magnesium sulfate are NMDA receptor antagonists. This study compared their effects on early postoperative negative emotions and pain in patients undergoing endoscopic sinus surgery (ESS).

Methods: This study involved 137 patients scheduled for ESS were randomly assigned to three groups: Group E (esketamine), Group M (magnesium sulfate), and Group C (saline control). Before induction, Group E received esketamine 0.25 mg/kg loading over 10 min then 0.25 mg/(kg·h) infusion until surgery end; Group M received magnesium sulfate 30 mg/kg loading over 10 min then 10 mg/(kg·h) infusion until surgery end; Group C received equal volume of normal saline. Hospital Anxiety and Depression Scale (HADS) and Self-rating Anxiety/Depression Scale (SAS/SDS) scores were assessed on postoperative days 1 and 2 (POD1, POD2). VAS scores, hemodynamics, intraoperative drug use, and adverse events were also evaluated.

Results: On POD1, HADS, SAS, and SDS scores were significantly lower in Groups E and M than in Group C ($P < 0.05$). On POD2, these scores were lower in Group E than in Groups C and M ($P < 0.05$). VAS pain scores were significantly lower in Groups E and M at 2, 4, and 8 hours postoperatively ($P < 0.001$). Remifentanyl consumption was lower in Groups E and M than in Group C ($P < 0.05$), nitroglycerin consumption was lower in Group M than in Group E ($P < 0.05$). Incidences of sore throat, rescue analgesia, postoperative respiratory depression, and PONV in Groups E and M were significantly lower than those in Group C ($P < 0.05$).

Conclusion: Intravenous esketamine or magnesium sulfate effectively alleviated negative emotions and pain on POD1 in patients undergoing ESS. Esketamine demonstrated superior efficacy over magnesium sulfate on POD2.

Keywords: esketamine, magnesium sulfate, anxiety, depression, postoperative pain, endoscopic sinus surgery

Introduction

In recent decades, modern anesthesiology has made significant progress in perioperative safety. However, under the current philosophy of enhanced recovery, it has become increasingly clear that physiological stability alone is not sufficient.¹ A growing body of evidence shows that perioperative negative emotions, especially anxiety and depressive symptoms, can lead to poorer outcomes.² Furthermore, these emotional disorders amplify pain perception, increase opioid requirements, provoke stress responses, delay mobilization, and even extend hospital stays, ultimately compromising postoperative quality of life.^{3–5} Therefore, developing comprehensive treatment strategies to improve and manage negative emotions during the perioperative period has become crucial for modern anesthesia management.

Chronic rhinosinusitis (CRS), with or without nasal polyps, is a common inflammatory disorder that substantially impairs quality of life. For medically refractory cases, ESS remains the standard of care.⁶ Yet despite its effectiveness in

restoring sinonasal function, the perioperative period carries a considerable psychological burden. Many patients present with preoperative anxiety and depression stemming from chronic nasal obstruction, sleep disturbance, and anticipatory distress over postoperative nasal packing.^{7,8} This packing-induced sensation of airway restriction can provoke dyspnea, which not only heightens psychological vulnerability but also lowers the pain threshold — conditions favorable to the development of central sensitization. Given that postoperative anxiety and depressive symptoms can persist beyond the immediate recovery period and affect long-term recovery, achieving sustained improvement in emotional outcomes is of particular clinical importance.

Addressing this burden requires an integrated approach to perioperative care that encompasses both somatic and psychological dimensions. NMDA receptor antagonists have attracted growing interest in this context, given their dual roles in analgesia and mood modulation. Esketamine, the S(+)-enantiomer of ketamine, binds NMDA receptors with greater affinity than the racemic mixture and exerts rapid antidepressant effects through the modulation of synaptic plasticity and brain-derived neurotrophic factor (BDNF) expression.⁹ Magnesium sulfate, a naturally occurring calcium antagonist and non-competitive NMDA receptor blocker, has likewise been used perioperatively to blunt the surgical stress response and maintain hemodynamic stability.¹⁰

Despite the established analgesic properties for both agents, direct comparative data on their capacity to attenuate the specific emotional distress associated with ESS are lacking. This randomized controlled trial therefore evaluated the effects of sub-anesthetic esketamine versus magnesium sulfate on early postoperative negative emotions and pain in patients undergoing ESS, to inform perioperative strategies for psychological recovery.

Materials and Methods

Study Design and Participants

This study was designed as a single-center, prospective, randomized, double-blind, parallel-group controlled trial. The protocol was reviewed and approved by the Ethics Committee of the Affiliated Huai'an Hospital of Xuzhou Medical University (Approval No. HEYLL202512). The trial was prospectively registered at ClinicalTrials.gov (Identifier: NCT06920576) before patient enrollment. All participants provided written informed consent prior to inclusion. The study was conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines.

A total of 144 patients scheduled to undergo elective ESS under general anesthesia at the Affiliated Huai'an Hospital of Xuzhou Medical University were screened for eligibility. Participants were eligible if they: (1) were 18–65 years old; (2) had an American Society of Anesthesiologists (ASA) physical status of I–II; (3) were scheduled for functional ESS or septoplasty under general anesthesia; (4) were able to provide informed consent and complete postoperative assessments. Patients were excluded if they had: (1) known allergy or contraindication to esketamine, magnesium sulfate, or any study-related anesthetic agents; (2) severe cardiac, hepatic, renal, or neurological disease; (3) pregnancy or lactation; (4) diagnosed psychiatric disorders, a history of substance abuse, or long-term psychotropic medication use; (5) poorly controlled hypertension, diabetes, or hyperthyroidism; (6) anticipated surgical duration > 2 h; (7) difficult airway requiring modified intubation techniques; (8) inability to comply with study procedures.

Randomization and Blinding

Eligible patients were randomly assigned to one of three groups: the esketamine group (Group E), the magnesium sulfate group (Group M), or the saline control group (Group C), with a distribution ratio of 1:1:1. Randomization was performed using sequentially numbered, opaque, sealed envelopes to conceal group allocation. To ensure allocation concealment, the randomization list was kept hidden from the anesthesiologists directly responsible for the patients' care and from those who would later assess the outcomes. All study drugs were prepared in identical syringes by an independent anesthesiologist not involved in further patient management, ensuring that the attending anesthesiologists, outcome assessors, and patients were blinded to the group assignments.

Anesthesia Protocol

All patients underwent routine preoperative preparation, namely, 8 hours of fasting and 2 hours of clear fluid restriction. No premedication was administered. Upon arrival in the operating room, standard monitoring was established, including non-invasive blood pressure (NIBP), pulse oximetry (SpO₂), electrocardiography (ECG), and entropy (State Entropy, SE; Response Entropy, RE). Core body temperature was maintained at approximately 37°C using a forced-air warming blanket. All patients received a slow intravenous injection of midazolam (0.05 mg/kg) prior to the start of the experiment. Subsequently, Group E received an initial bolus of 0.25 mg/kg esketamine over 10 minutes before induction, followed by a continuous infusion at 0.25 mg/(kg·h) until the end of surgery. Group M received an initial bolus of 30 mg/kg magnesium sulfate over 10 minutes before induction, followed by a continuous infusion at 10 mg/(kg·h) until the end of surgery; Group C received an equivalent volume of saline via infusion during the same time period.

All patients underwent a standardized induction protocol: propofol (1.5 mg/kg), sufentanil (0.5 µg/kg), and rocuronium bromide (0.6 mg/kg). After adequate muscle relaxation was achieved, endotracheal intubation was performed, and mechanical ventilation was initiated using an anesthesia machine. The ventilation parameters were set as follows: tidal volume 6–8 mL/kg, inspiratory-to-expiratory ratio 1:2, and end-tidal carbon dioxide pressure (P_{ET}-CO₂) maintained within 35–40 mmHg. Anesthesia was maintained with continuous infusions of propofol (4–12 mg/kg/h) and remifentanyl (0.1–0.5 µg/kg/min). Dosages were adjusted in real time based on the entropy index (RE/SE) to maintain the anesthesia depth between 40 and 60. Vasoactive agents were administered intraoperatively as needed to limit mean arterial pressure (MAP) fluctuations to within 20% of baseline values and maintain the heart rate (HR) between 50–100 beats per minute. Postoperatively, all patients were transferred to the postanesthesia care unit (PACU) for observation and recovery management. In the PACU, pain intensity was periodically assessed using the Visual Analog Scale (VAS; 0–10 points). Patients with VAS scores > 3 received 30 mg intravenous ketorolac tromethamine for rescue analgesia.

Data Collection and Outcome Assessment

We used standardized forms to obtain baseline characteristics from the clinical record, including demographic characteristics and intraoperative data, as well as a history of smoking and hypertension. In order to ensure data accuracy and consistency, we had a trained investigator handle part of the process. This investigator was blinded to group allocation. During the preoperative visit, they provided standardized education to every patient and their families. The investigator thoroughly explained the scoring procedures for each questionnaire and verified that all items were clearly understood by the participants. Preoperative and postoperative assessments were conducted in the ward on the designated days to standardize data collection and minimize temporal variability.

The primary outcome measures of this study were the Hospital Anxiety and Depression Scale (HADS) scores, assessed on postoperative day 1 (POD1) and day 2 (POD2). The secondary outcomes included the following: (1) Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) scores on POD1 and POD2; (2) postoperative pain intensity, we measured using a Visual Analog Scale (VAS) at 2, 4, 8, 24, and 48 hours after surgery; (3) hemodynamic parameters (MAP and HR) recorded at specific time points: T0, upon entering the operating room; T1, before intubation; T2, after intubation; T3, at the end of surgery; T4, after extubation. (4) intraoperative consumption of propofol, remifentanyl, and vasoactive agents; (5) time to recovery of consciousness and extubation; incidence of postoperative sore throat; and requirement for rescue analgesia (intravenous ketorolac tromethamine 30 mg for VAS > 3); (6) incidence of adverse events within 48 hours postoperatively, including postoperative nausea and vomiting (PONV), respiratory depression, dizziness, headache, hallucinations, diplopia, and nightmares.

Sample Size Calculation

The sample size was calculated using PASS software (version 15.0). According to our pilot study, calculation based on the difference in HADS-A score before and 2 days after surgery. The mean HADS-A score difference among the three groups were 3.6, 2.8, and 3.4, with corresponding standard deviations of 0.92, 0.99, and 1.07, respectively. To achieve 90% power and a two-tailed significance level of 0.05, a total of 112 patients was needed for this study. Accounting for a potential 20% loss to follow-up or withdrawal of consent, 48 patients per group were enrolled in the trial (total n = 144).

Statistical Analysis

Continuous variables that followed a normal distribution were presented as mean $\pm$ standard deviation (SD). For normally distributed outcome measures with a repeated-measures structure (including SAS, SDS, and the hemodynamic parameters MAP and HR), a mixed-effects model for repeated measures (RM ANOVA) was used. The interaction F -value and its P value were reported. Post hoc comparisons were performed with Bonferroni correction. The primary focus was on the group-by-time interaction effect, followed by the main effects of group and time. Between-group comparisons were conducted using one-way analysis of variance (ANOVA), with post hoc pairwise comparisons adjusted by Bonferroni correction. Within-group comparisons across different time points were performed using repeated-measures ANOVA. For variables that did not follow a normal distribution (HADS, VAS), data were presented as median (interquartile range). A generalized estimating equation (GEE) or linear mixed model (LMM) was applied to simultaneously evaluate between-group differences, time trends, and their interaction. For between-group comparisons at each time point, the Kruskal–Wallis H -test was used. Categorical variables were expressed as n (%) and analyzed using the chi-square test. A two-sided P value < 0.05 was considered statistically significant.

Missing data occurred in 7/144 patients (4.86%), with a balanced distribution across groups. Given the low missing rate ($< 5\%$) and the clear missing pattern, no multiple imputation was applied. A worst-case imputation sensitivity analysis confirmed the robustness of the per-protocol results.

Results

Patient Enrollment and Baseline Characteristics

A total of 144 patients were initially enrolled. Two patients in Group C and two in Group M withdrew due to incomplete questionnaire assessments. Two patients in Group E and one in Group C were excluded because of refractory hypertension requiring repeated vasoactive interventions. Thus, 137 patients completed the study and were included in the final analysis: 45 in Group C, 46 in Group E, and 46 in Group M (Figure 1). Baseline demographic variables and intraoperative characteristics were comparable among the three groups, with no statistically significant differences (Table 1).

Hospital Anxiety and Depression Scale (HADS)

GEE revealed significant group $\times$ time interaction effects for both HADS-A and HADS-D scores (HADS-A: $\chi^2 = 83.443$, $P < 0.001$; HADS-D: $\chi^2 = 44.244$, $P < 0.001$). At POD1, Group E and Group M showed lower HADS-A and HADS-D scores compared with Group C (all $P < 0.01$). On POD2, only Group E maintained a significant reduction in HADS-A and HADS-D scores relative to Group C (all $P < 0.001$). In the intervention group comparisons, Group E had a lower HADS-A score than Group M on POD1 ($P = 0.004$). On POD2, Group E exhibited significantly lower scores in both HADS-A and HADS-D compared with Group M (both $P < 0.001$) (Figure 2).

SAS and SDS

RM ANOVA revealed significant group $\times$ time interaction effects for both SAS and SDS scores (SAS: $F = 30.393$, $P < 0.001$; SDS: $F = 30.490$, $P < 0.001$). Consistent with the HADS results, SAS and SDS scores on POD1 were significantly lower in both Group E and Group M than in Group C (all $P < 0.01$). On POD2, only Group E continued to demonstrate significantly reduced SAS and SDS scores compared with Group C (all $P < 0.001$). Direct comparison between the two intervention groups showed that Group E had significantly lower SAS and SDS scores than Group M on both POD1 (SAS: $P = 0.025$; SDS: $P = 0.010$) and POD2 (both $P < 0.001$) (Figure 3).

Postoperative Pain (VAS)

Analysis using GEE revealed a significant group $\times$ time interaction effect for VAS scores ($\chi^2 = 44.679$, $P < 0.001$). At 2, 4, and 8 hours postoperatively, VAS scores were significantly lower in both Group E and Group M than in Group C (all $P < 0.001$), with no significant difference between the two treatment groups ($P > 0.05$). At 24 and 48 hours postoperatively, there were no significant differences in VAS scores among the three groups ($P > 0.05$) (Table 2).

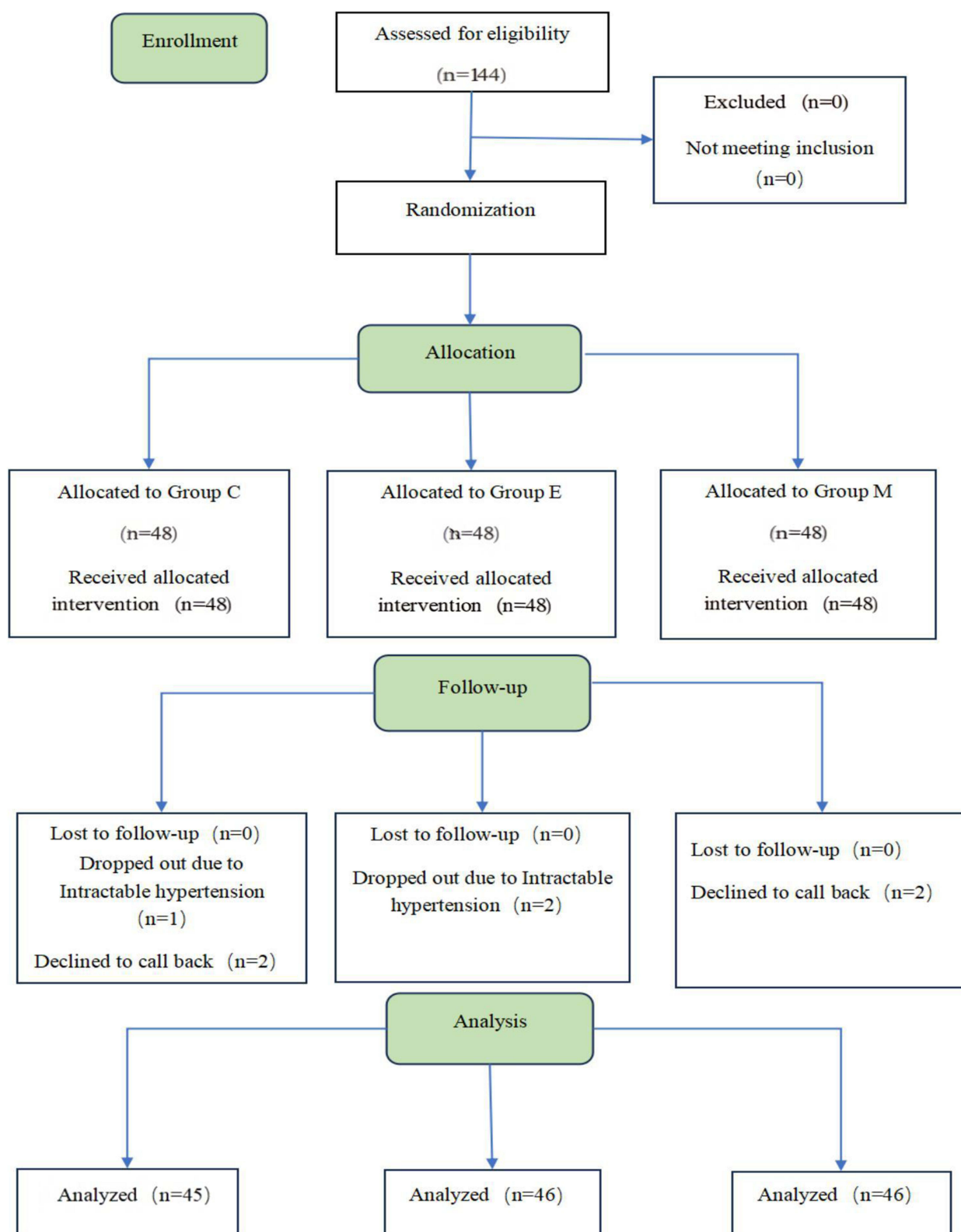


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1 Patient Demographic Characteristics and Intraoperative Data

	Group C (n=45)	Group E (n=46)	Group M (n=46)	P value
Age (years)	45.16±9.59	43.70±11.04	42.33±11.69	0.461
Gender (Male/Female)	28/17	25/21	25/21	0.682
Height (cm)	170.27±7.37	169.17±6.68	170.28±5.10	0.641
Weight (kg)	69.84±7.52	69.15±10.14	71.15±8.87	0.552
BMI (kg/m ²)	24.05±1.62	24.12±2.97	24.53±2.84	0.623
ASA physical Status (I/II)	36/9	38/8	37/9	0.944
Smoking (yes/no)	10/35	11/35	13/33	0.789
Hypertension (yes/no)	6/39	8/38	6/40	0.805
History of motion sickness (yes/no)	2/43	2/44	1/45	0.807
Surgery type				0.935
Sinusitis	29	30	33	
Nasal Polyps	9	10	8	
Nasal Septum	7	6	5	
Mean duration of surgery (min)	52.44±13.62	53.78±14.07	53.67±12.88	0.872
Mean duration of anesthesia(min)	69.71±12.65	72.11±13.34	72.48±10.05	0.499

Note: Data are expressed as mean ± standard deviation or number of patients.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Haemodynamic Responses (MAP and HR)

RM ANOVA revealed that neither MAP nor HR exhibited a significant group × time interaction effect (MAP: $F = 6.506$, $P = 0.120$; HR: $F = 6.512$, $P = 0.091$). At T2 (post-intubation), Group E had higher MAP and HR compared with both Group C and Group M (all $P < 0.05$). There were no significant between-group differences at T0, T1, T3, or T4 ($P > 0.05$) (Figure 4).

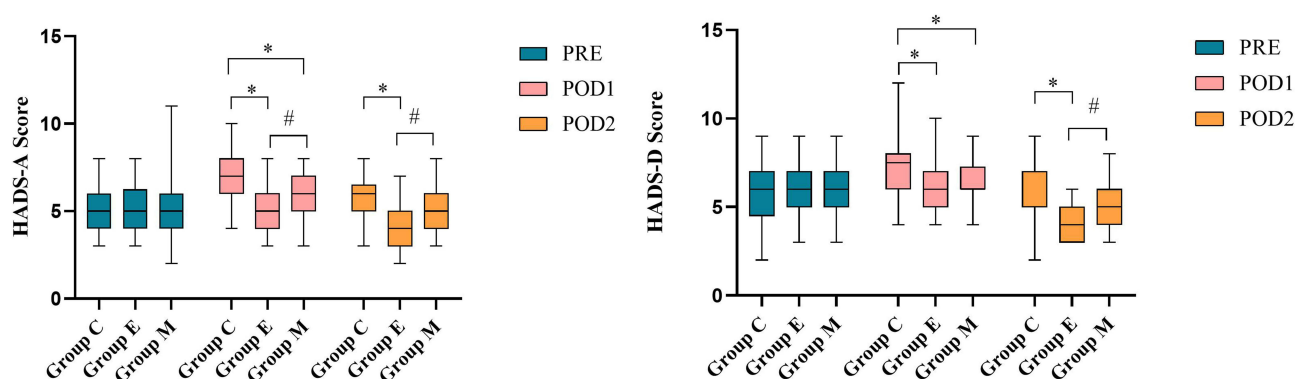


Figure 2 Hads scores. * $P < 0.05$ for comparison with Group C; # $P < 0.05$ for comparison with Group M.

Abbreviations: PRE, the day before surgery; POD1, postoperative day 1; POD2, postoperative day 2; HADS-A, Hospital Anxiety and Depression Scale Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale Depression subscale.

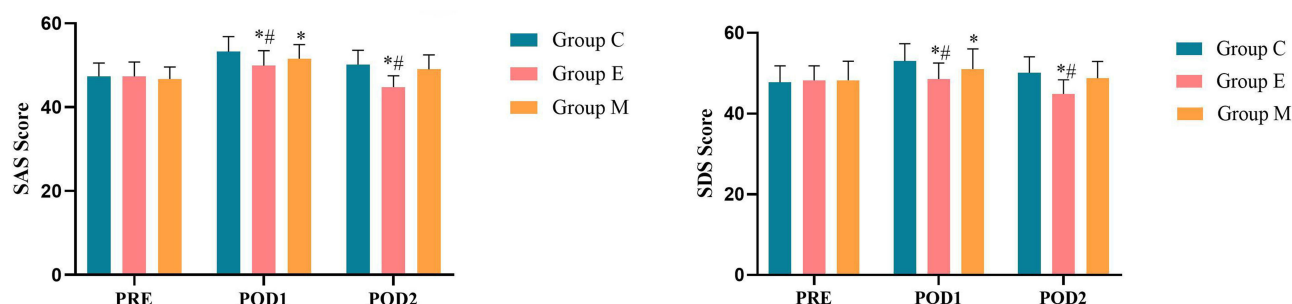


Figure 3 SAS and SDS scores. * $P < 0.05$ for comparison with Group C; # $P < 0.05$ for comparison with Group M.

Abbreviations: SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; PRE, the day before surgery; POD1, postoperative day 1; POD2, postoperative day 2.

Table 2 VAS Scores

	Group C (n=45)	Group E (n=46)	Group M (n=46)	P value
VAS scores				
2 h	3 (2, 3.5)	2 (1, 2)*	2 (2, 3)*	<0.001
4 h	4 (4, 5)	2 (2, 3)*	3.5 (3, 4)*	<0.001
8 h	3 (3, 3)	2 (2, 2)*	2 (2, 3)*	<0.001
24 h	2 (2, 2)	2 (1, 2)	2 (1, 2)	0.072
48 h	2 (1, 2)	1.5 (1, 2)	1.5 (1, 2)	0.665

Notes: Data are expressed as median (interquartile range, IQR), * $P < 0.05$ for comparison with Group C.

Intraoperative Drug Consumption and Recovery Profiles

Compared with Group C, both Group E and Group M required significantly less remifentanyl intraoperatively ($P < 0.05$). Propofol consumption did not differ among the three groups ($P > 0.05$).

Nitroglycerin usage was significantly lower in Group M than in Group E ($P < 0.05$). No significant differences were noted in epinephrine use across groups ($P > 0.05$). Recovery time and extubation time were comparable among the three

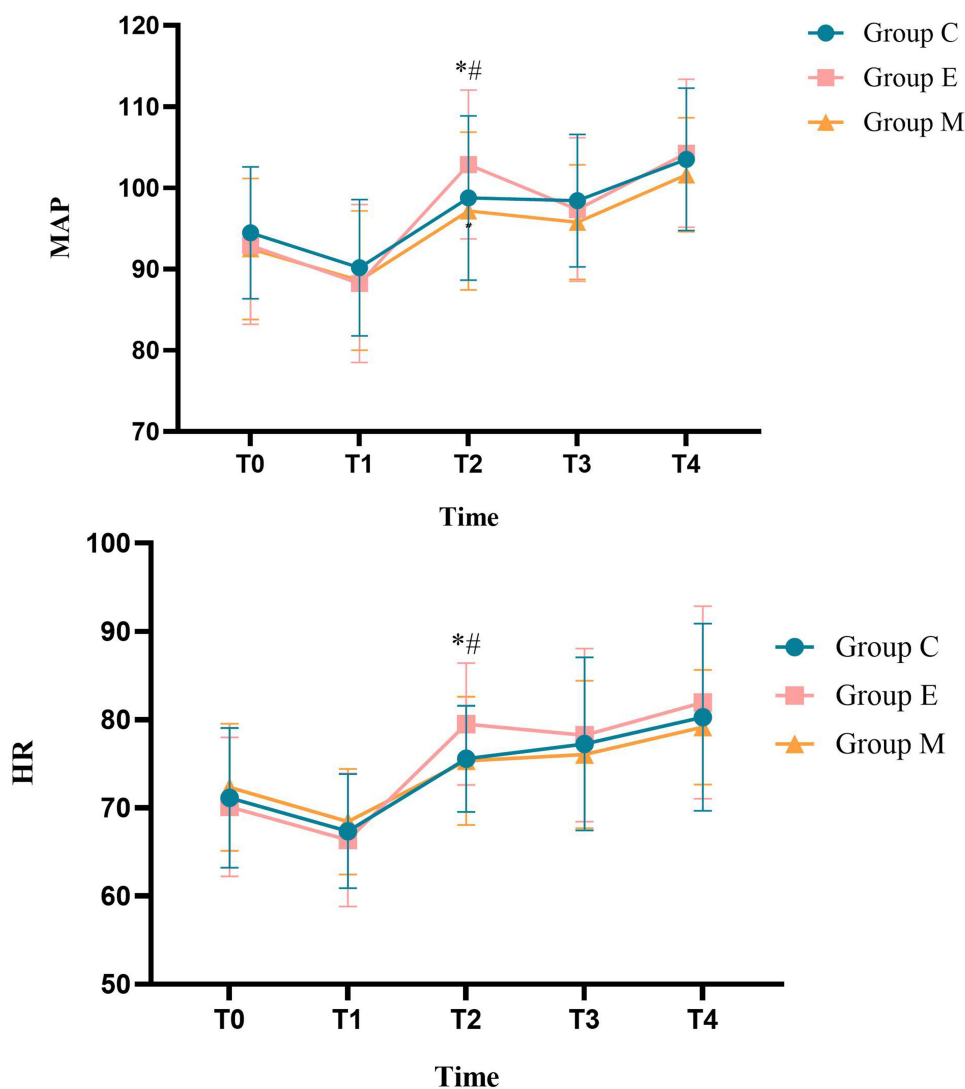


Figure 4 HR and MAP. * $P < 0.05$ for comparison with Group C; # $P < 0.05$ for comparison with Group M.

Abbreviations: HR, heart rate; MAP, mean arterial pressure; T0, upon entering the operating room; T1, before intubation; T2, after intubation; T3, at the end of surgery; T4, after extubation.

Table 3 Intraoperative and Postoperative Indicators

	Group C (n=45)	Group E (n=46)	Group M (n=46)	P value
Propofol (mg)	375.33±79.05	355.22±72.13	367.61±72.39	0.432
Remifentanyl (μg)	406.67±60.79	357.83±55.25*	376.52±53.92*	<0.001
Nitroglycerine (μg)	40 (0, 60)	40 (0, 80) #	0 (0, 40)	0.021
Phenylephrine (μg)	0 (0, 50)	0 (0, 50)	0 (0, 50)	0.657
Awakening time (min)	23.24±3.41	23.35±3.03	23.07±3.23	0.914
Extubation time (min)	25.58±3.66	24.48±2.59	24.78±2.97	0.222
POST (n%)	10 (22.2%)	2 (4.3%)*	4 (8.7%)*	0.023
Number of requiring rescue analgesia (n%)	9 (20%)	2 (4.3%)*	3 (6.5%)*	0.029

Notes: Data are expressed as mean ± standard deviation or median (interquartile range, IQR) or number (n%), * $P < 0.05$ for comparison with Group C; # $P < 0.05$ for comparison with Group M.

Table 4 Postoperative Adverse Reactions

	Group C (n=45)	Group E (n=46)	Group M (n=46)	P value
PONV (n%)	6 (13.3%)	1 (2.2%)*	1 (2.2%)*	0.033
Respiratory depression (n%)	5 (11.1%)	0 (0%)*	1 (2.2%)*	0.023
Dizziness or headache (n%)	2 (4.4%)	1 (2.2%)	1 (2.2%)	0.760
Hallucinations or double vision (n%)	0 (0%)	1 (2.2%)	0 (0%)	0.369
Hypersomnia (n%)	1 (2%)	1 (2.2%)	0 (0%)	0.599
Nightmares (n%)	0 (0%)	0 (0%)	0 (0%)	>0.99
Flushing (n%)	0 (0%)	0 (0%)	0 (0%)	>0.99
Dry mouth (n%)	0 (0%)	1 (2.2%)	1 (2.2%)	0.609
Sweating (n%)	0 (0%)	0 (0%)	1 (2.2%)	0.369

Notes: Data are expressed as number (n%),* $P < 0.05$ for comparison with Group C.

groups ($P > 0.05$). The incidence of postoperative sore throat and the need for rescue analgesia were significantly lower in Groups E and M compared with Group C ($P < 0.05$) (Table 3).

Adverse Events

Both Group E and Group M showed significantly lower incidences of postoperative nausea/vomiting and respiratory depression compared with Group C ($P < 0.05$). No significant differences were observed among the three groups regarding dizziness or headache, hallucinations or diplopia, drowsiness, nightmares, flushing, dry mouth, or sweating ($P > 0.05$) (Table 4).

Discussion

In this prospective, randomized, double-blind controlled trial, we found that both esketamine and magnesium sulfate reduced early postoperative anxiety, depression, and pain in patients undergoing ESS on POD1. Between the two, esketamine showed greater efficacy in attenuating postoperative negative emotions and pain on POD2. Both agents also lowered intraoperative remifentanyl consumption and decreased the incidence of PONV and respiratory depression, without increasing the overall rate of adverse events.

The high prevalence of postoperative negative emotions and their clear detrimental effect on recovery has been described in many surgical areas.^{11,12} For patients with CRSwNP, it has also been reported that reducing negative emotions may help lower perioperative stress and promote faster postoperative recovery.¹³ Although most existing clinical data focus on esketamine, studies on magnesium sulfate and its effect on perioperative mood are still quite limited. However, in our study, we found that both perioperative esketamine and magnesium sulfate improved postoperative mood and reduce pain. A recent large meta-analysis, which included 16 randomized controlled trials ($n = 1161$ esketamine; $n = 1106$ control), showed that perioperative esketamine significantly reduced postoperative depression scores and improved pain outcomes, while not increasing adverse events such as

PONV, dizziness, nightmares, or dissociation.¹⁴ In addition, other studies have reported that intravenous esketamine improves early postoperative recovery quality, reduces pain at 24 hours, lowers PONV incidence, improves sleep, and increases Quality of Recovery-15 (QoR-15) and Quality of Recovery-40 (QoR-40) scores.^{15,16} In our study, we also observed lower VAS scores, less opioid use, and fewer cases of PONV and respiratory depression in both the esketamine and magnesium sulfate groups.

The antidepressant and anxiolytic effects of these two agents, especially those of esketamine, seem quite consistent with their known mechanisms. Esketamine is a potent NMDA receptor antagonist, and it is believed to rapidly reverse stress-related synaptic deficits and help restore neural circuit function, which is central to its antidepressant action.^{17,18} Luo et al reported that esketamine reduced postoperative anxiety and depression in patients undergoing non-cardiac thoracic surgery, which is consistent with the significant improvement in HADS, SAS, and SDS scores we observed in our study.¹⁹ Notably, in our study, the HADS, SAS, and SDS scores in the esketamine group were lower than those in the magnesium sulfate group on postoperative day 2. Although this difference was statistically significant and the effect size was large, the absolute difference did not reach the minimum clinically important difference (MCID).²⁰ These findings warrant further validation in larger sample sizes or in different clinical settings.

Regarding analgesia, both groups showed a clear reduction in early postoperative VAS scores and a lower need for rescue analgesia. This is consistent with the expectation that NMDA receptor antagonism plays a central role in preventing or limiting central sensitization.^{21,22} Although esketamine did not demonstrate a statistically significant increase in analgesic efficacy at 24 and 48 hours postoperatively, it showed a significant trend toward lower pain levels compared with magnesium sulfate, suggesting potential clinical significance. Further validation of its long-term analgesic effects is warranted in future studies with a larger sample size. This may be related to its multimodal actions, including not only NMDA receptor blockade, but also its impact on monoamine pathways and some interactions with opioid receptors.²³ In addition, esketamine's anti-inflammatory and neuroprotective properties may also have contributed to analgesia. These mechanisms may help reduce neuroinflammatory reactions after surgical trauma, which in turn may help interrupt the cycle of pain and negative emotions reinforcing each other.¹⁸ Magnesium sulfate, while clearly effective in the early postoperative stage, probably relies mainly on NMDA receptor blockade and calcium channel antagonism. This mechanism is helpful, but it may not provide the same long-lasting benefits as esketamine. In our data, this difference was quite noticeable after the first postoperative day, which seems to align with the pharmacological profiles of the two drugs.

ESS requires a highly clear surgical field, and intraoperative vasoconstrictors such as epinephrine are commonly used to control bleeding; however, these agents can induce significant hemodynamic fluctuations. Our study found that during endotracheal intubation, esketamine caused a transient increase in MAP and HR, consistent with its sympathomimetic properties. Nevertheless, the overall trends in MAP and HR over time were similar across the three groups (interaction effect $P > 0.05$), indicating that the effects of esketamine were limited to transient fluctuations at specific time points. In contrast, patients receiving magnesium sulfate or saline showed no significant differences in MAP or HR at any time point, and no pronounced fluctuations occurred after intubation. Although some studies have reported that intravenous magnesium sulfate can alleviate hemodynamic changes during laparoscopic surgery and attenuate the sympathetic response to surgical trauma,²⁴ the results of our study demonstrate that among ESS patients requiring strict intraoperative blood pressure control, the overall perioperative hemodynamic trends were similar across the three groups, and magnesium sulfate demonstrated no clear advantage in maintaining hemodynamic stability.

The reduction in PONV and respiratory depression observed in both intervention groups is a meaningful clinical finding. The most straightforward explanation is the clear decrease in intraoperative remifentanyl use, since opioid-sparing remains one of the main strategies for lowering dose-dependent opioid-related adverse events.²⁵ It is also worth noting that, at the doses and infusion rates used in our protocol, neither esketamine nor magnesium sulfate led to an increased incidence of other adverse effects, such as psychotomimetic symptoms with esketamine or flushing and palpitations with magnesium sulfate.²⁶ This indicates that, with careful titration, both drugs can be safely integrated into a balanced anesthetic technique for patients undergoing ESS.

In clinical practice, esketamine may be preferred for patients with preoperative anxiety, depressive tendencies, or a high risk of postoperative emotional disturbances, as well as for those requiring potent, long-lasting analgesia and reduced opioid consumption.^{27,28} In contrast, magnesium sulfate may be the preferred option for patients with preoperative hypertension or those requiring strict hemodynamic control (eg, those with a history of coronary heart disease or cerebrovascular disease).²⁹ In well-resourced medical centers, prioritizing esketamine for ESS patients

at high risk of emotional disturbances demonstrates favorable clinical value and cost-effectiveness. However, in resource-limited settings or for patients with significant cardiovascular risks, magnesium sulfate remains a safe, effective, and economical alternative.^{30,31}

There are several limitations that should be considered. First, as a single-center study, the sample size might be insufficient, and large, and multicenter studies are needed to make the results more robust. Second, our follow-up period was restricted to the early postoperative stage, and we still do not know the medium- or long-term effects on mood or functional recovery. Third, we did not include mechanistic biomarkers, such as inflammatory cytokines, which could have provided additional support for the proposed neuroplastic and anti-inflammatory pathways. Finally, our dosing regimens were fixed, so we could not explore dose–response relationships or determine the most appropriate infusion duration.

Conclusions

In this double-blind, randomized controlled trial, we found that intravenous esketamine or magnesium sulfate was effective in alleviating postoperative anxiety, depression, and pain in patients undergoing ESS on POD1. On POD2, esketamine was more effective than magnesium sulfate in improving postoperative anxiety and depression. Our findings support the inclusion of NMDA receptor antagonists as adjuncts in the multimodal management of patients undergoing ESS to facilitate “psychosomatic” recovery.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of the Affiliated Huai'an Hospital of Xuzhou Medical University (Approval No. HEYLL202512) and was registered at ClinicalTrials.gov (Identifier: NCT06920576). Written informed consent was obtained from all patients to publish this article in accordance with the journal's patient consent policy. The study was conducted in accordance with the Declaration of Helsinki and adhered to the CONSORT guidelines.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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