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CLINICAL TRIAL REPORT

Effect of Preoperative Esketamine Nebulized Inhalation on Cough Reflex, Sedation, and Postoperative Sore Throat in Extubation of Surgical Patients: A Prospective, Double-Blind, Randomized Controlled Trial

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Purpose: This study aims to explore the effect of preoperative esketamine nebulized inhalation on cough reflex during extubation for surgical patients who received general anesthesia.

Patients and methods: A total of 84 patients scheduled for thoracolumbar spine surgery were included in the study. All patients were randomly divided into two groups. Patients in the experimental group (Group K) received 5 mL of esketamine solution (50 mg esketamine + 3 mL of saline) by nebulized inhalation for 15 minutes. Patients in the control group (Group S) received an equal volume of saline as placebo. The incidence and intensity of the cough reflex were evaluated. The Riker Sedation-Agitation Scale score, Ramsay sedation score, and Monitoring of sore throat following surgery were performed at 0, 2, 4, 6, 12, and 24 hours post-surgery.

Results: The incidence of cough reflex was lower in Group K (31.0%) than in Group S (71.4%), and cough intensity was milder in Group K than in Group S ($P<0.001$). The Ramsay sedation scale score post-extubation was higher in Group K than in Group S ($P=0.002$). The incidence and severity of postoperative sore throat in Group K were lower than in Group S at 2, 4, 6, 12, and 24 hours following extubation (all $P<0.05$).

Conclusion: Preoperative esketamine nebulized inhalation has a potential inhibitory effect on the cough reflex during extubation for patients who received general anesthesia via tracheal intubation.

Keywords: esketamine, nebulized inhalation, cough reflex, tracheal extubation

Introduction

Coughing serves as a protective reflex of the respiratory system, commonly triggered by mechanical or chemical stimuli that activate the peripheral sensory nerve endings under the mucous membranes of the pharynx, larynx, and trachea.[1] Signals are transmitted to the brainstem's cough center through the vagus nerve. Once integrated, the outgoing signals are dispatched to the effectors, triggering the cough reflex.[2] However, the cough reflex induced by tracheal extubation following general anesthesia is one of the most frequent undesirable phenomena in clinical practice.[3,4] It causes intense discomfort to patients and increases the risk of adverse events, such as blood leakage from surgical incision, airway

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spasm, and hemodynamic instability.[5,6] In thoracolumbar surgeries, these complications may lead to postoperative bleeding, acute upper airway obstruction, and an increased risk of reoperation.[7,8]

Approaches to suppress the cough reflex during extubation have included both medication and non-medication techniques, which have met with varying success. Non-medication techniques included gargling with 4 mg azunol diluted in 100 mL tap water, gargling with 0.5 g of licorice in 30 mL of water, or using licorice lozenges.[9] However, there is currently insufficient evidence to determine whether these measures offer comparable or superior effectiveness in reducing coughing during extubation compared to other interventions. In contrast, several medications have demonstrated more defined efficacy. For instance, intravenous lidocaine has been shown to significantly reduce cough at extubation.[10] A continuous infusion of 0.2μg/kg/min remifentanil during the peri-extubation period can effectively suppress stress and cough reflexes.[11] BIS-guided sedation with dexmedetomidine and propofol reduces the cough reflex caused by suctioning or extubation during the recovery from general anesthesia.[12] However, these drug-based treatments come with certain side effects. For instance, intravenous injection of lidocaine may prolong the extubation and recovery time, while remifentanil may lead to respiratory depression and delayed awakening.[13] A network meta-analysis comparing various intervention measures (including lidocaine, dexmedetomidine, fentanyl, and remifentanil) concluded that dexmedetomidine was the most effective in reducing the incidence of severe cough during extubation. However, it may cause some side effects, such as prolonged sedation or bradycardia.[14]

As N-methyl-D-aspartate (NMDA) receptor antagonists, ketamine and esketamine are used in anesthetic practice and possess unique properties that may effectively suppress cough. Evidence suggests that NMDA receptor antagonists not only play a critical role in regulating the cough reflex but also exert a direct relaxant effect on airway smooth muscles.[15] Moreover, compared with other drugs, they can also reduce remifentanil-induced hyperalgesia by inhibiting NMDA receptors, thereby decreasing postoperative pain and opioid consumption.[16] However, ketamine's psychomimetic side effects have limited its widespread clinical use. Esketamine, the right-handed enantiomer of ketamine, exhibits comparable pharmacological properties. Studies have shown that esketamine has approximately two to four times stronger affinity for NMDA receptors than ketamine.[17] Moreover, esketamine is metabolized more quickly than ketamine and has minimal side effects.[18,19] Although several studies have suggested using mouth rinsing as the administration method, we chose to use the nebulization method instead. In a study involving healthy volunteers, no respiratory adverse events occurred during or after esketamine inhalation.[20] Nebulized inhalation ensures that the drug is evenly and effectively distributed throughout the throat area and reaches the starting point of the respiratory tract. Moreover, inhalation can avoid the problem of individual differences caused by mouth rinsing, and it also eliminates the discomfort caused by the taste of the drug.[21] Applying ketamine locally helps protect against airway inflammation through interference with Ca^{++} and relaxing airway smooth muscle.[22]

In our study, we aimed to examine the effect of preoperative esketamine nebulized inhalation on the cough reflex during tracheal extubation in patients undergoing thoracolumbar spine surgery. We hypothesized that this intervention would successfully inhibit the cough reflex during tracheal extubation.

Methods

The underlying protocol follows the CONSORT Checklist (S1 checklist)

Study Design

This prospective, double-blind, randomized controlled trial was conducted in accordance with the CONSORT guidelines and received approval from the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2024-03-99). Written informed consent was provided by the patients or their relatives before the study was conducted. This study was registered in the Chinese Clinical Trial Registry (ChiCTR2400086812). The study adhered to the intention-to-treat principle for the primary outcome analysis, including all randomized patients. Patients with major protocol deviations were to be withdrawn, and the events along with their data were recorded and assessed by the investigators.

Study Participants

The research involved patients between 18 and 65 years old with American Society of Anesthesiologists (ASA) I-III, who were scheduled for thoracolumbar spine surgery. Patients who underwent thoracolumbar spine surgery were more likely cough during the recovery period compared to those who underwent supine surgery, as secretions accumulated in the pharynx and tracheal tube after prolonged periods of prone position.[23] The exclusion criteria were the absence of informed consent; mental or language barriers; existing severe cardiovascular disease, severe respiratory disease, and throat disease; abnormal lung function; allergy or contraindication to esketamine; and preoperative opioid use.

Randomization and Blinding

In this phase, all patients were randomly assigned to either the esketamine nebulized inhalation group (Group K) or the normal saline nebulized inhalation group (Group S) using block randomization. The random sequence was computer-generated by an anesthesiologist not involved in the study and concealed in opaque, sealed envelopes by a second independent anesthesiologist. The nurse who opened the envelopes in the medication preparation room and prepared the corresponding nebulization solutions took no part in subsequent patient assessments. To ensure the integrity of the double-blind design, the esketamine and placebo (normal saline) solutions were made indistinguishable in appearance. Consequently, all patients, anesthesiologists, surgeons, and postoperative follow-up staff remained blinded to group assignment throughout the study.

Anesthesia Protocol

On the surgery day, all patients were transferred to the pre-anesthesia preparation room. A 50 mg dose of esketamine was chosen based on pre-experiment, where a 75 mg dose caused significant hypertension in patients. According to group allocation, the nurse prepared 5 mL of nebulization solution for each patient. Patients in Group S received 5 mL of normal saline, while those in Group K received 50 mg of esketamine (2 mL) diluted with 3.0 mL of normal saline to a total volume of 5 mL. Patients in both groups received the nebulized solution using the same device: a mask connected to a wall-mounted oxygen source (8 L, 50 psi) for a duration of 15 min.

Following completion of nebulization, all patients were transferred to the operating room for standardized anesthesia management and routine monitoring. This includes invasive arterial pressure, heart rate (HR), electrocardiogram (ECG), peripheral oxygen saturation (SpO_2), body temperature, and bispectral index (BIS). Anesthesia was induced intravenously with midazolam (0.05 mg/kg), propofol (0.2 mg/kg), sufentanil (0.5 μg/kg), and cisatracurium (0.2–0.4 mg/kg). After 3 min, tracheal intubation was performed by an independent anesthesiologist with over a decade of experience, who was blinded to group allocation. The depth of catheter insertion was calculated transorally, and the distance from the tip of the tracheal tube to the upper incisors was measured at approximately 23 cm for men and 21 cm for women. After tracheal intubation, all patients underwent volume-controlled ventilation using an anesthesia machine. A balloon pressure gauge was used to check whether the tracheal catheter sleeve pressure was maintained at 25 cmH_2O. Propofol 4–8 mg/kg/h and remifentanil 0.1–0.3 μg/kg/min were continuously infused to maintain the BIS value at 40–60. Muscle relaxation is maintained through intermittent doses of cisatracurium. Furthermore, blood pressure and heart rate (HR) were maintained at the basic value of ±20% during the operation.

Postoperative Management

After surgery, patients were transferred to the post-anesthesia care unit (PACU). Before tracheal extubation, neuromuscular blockade was neutralized with atropine (0.5 mg) and neostigmine (1 mg). The criteria for removing the endotracheal tube include the patient's ability to follow simple instructions, recovery of swallowing and cough reflexes, a spontaneous breathing rate between 12 and 20 breaths/min, tidal volume > 6mL/kg, SpO_2 above 95% for five minutes, and stable hemodynamics.[24,25] The extubation procedure was performed by a team of uniformly trained anesthesia nurses under the anesthesiologist's guidance, adhering to a standardized protocol (pre-oxygenation with 100% oxygen, suctioning of the airway as needed, placement of a bite block and positioning of the patient appropriately, antagonism of neuromuscular blockade, confirmation of regular spontaneous breathing and adequate ventilation, application of positive

pressure at the end of expiration, followed by deflation of the endotracheal tube cuff and removal of the tube, immediate administration of 100% oxygen post-extubation, with assessment of airway patency and adequacy of ventilation). If a severe and persistent cough reflex occurred during emergence, intravenous lidocaine (1 mg/kg) was administered; the tracheal tube cuff was then slowly deflated and the tube removed. Patients were discharged from the PACU upon achieving an Aldrete score of 9. All outcome assessments and data collection followed a standardized protocol and were performed by three staff members (anesthesiologist, nurse, and assistant) who were blinded to group allocation and involved in different stages of the process. All surgical procedures were performed by the same team.

Data Collection

The primary outcome was the incidence of cough reflex. The secondary outcomes included cough intensity within 5 min of extubation, which was defined as follows: 0, no cough; 1, minimal (single) cough; 2, moderate (≤5 s) cough; and 3, severe (>5 s) cough (bucking).[26] The degree of emergence agitation was evaluated using the Riker Sedation-Agitation Scale score: 1 (unwakeable) to 7 (dangerous restlessness).[27] Meanwhile, the sedation levels were assessed using the Ramsay sedation scale (RSS), with scores ranging from 1 (anxious and agitated) to 6 (no response to stimuli).[28] During the extubation procedure, the nurses in the PACU gathered the outcomes that were previously mentioned. The mean arterial pressure (MAP) and heart rate (HR) were collected by the anesthesiologist in the pre-anesthesia preparation room, the operating room, and the PACU at the following time points: before nebulized inhalation (T0), at the end of nebulized inhalation (T1), after the completion of anesthesia induction (T2), upon PACU admission (T3), immediately after extubation (T4), 10 min after extubation (T5), and discharged from the PACU (T6). Postoperative sore throat (POST) was evaluated by a research assistant using a numeric rating scale from 0 (no sore throat) to 10 (worst imaginable pain).[29] The assessment time points were 0, 2, 4, 6, 12, and 24 hours after extubation. According to previous literature,[30] this study also focused on the adverse reactions associated with esketamine, including confusion, hallucinations, nausea and vomiting. The postoperative complications mentioned above were collected by a study assistant in the ward during the first three days after surgery and upon discharge.

Sample Size Calculation

In a former study,[31] the incidence of cough reflex in recovery without intervention was 66.7%, and esketamine nebulization was thought to reduce such incidence to 35% and the α of 0.05, with 36 patients needed in each group (with the power of 0.80). Considering the potential dropout during postoperative follow-up and refusing to continue participating in the study, the required sample size was increased to 42 patients per group.

Statistical Analysis

All statistical analyses were performed with SPSS software (version 16.0; IBM Corp). In this study, continuous data with normal distribution were shown as mean ± standard deviation and compared between the groups with independent samples *t*-test. Continuous data that do not conform to the normal distribution are expressed as median and range, and the differences between the two groups are examined by Mann–Whitney U-test. Categorical variables were outlined as percentages or numbers, and comparisons between groups were done with chi-squared (χ^2-test) or Fisher's exact tests. Repeated measures analysis of variance was used to compare data at multiple time points between the two groups. $P < 0.05$ was considered to be statistically significant.

Results

Out of 123 consecutive patients in this study, 84 met the criteria and were enrolled. The remaining 39 were excluded (27 did not meet the inclusion criteria, 10 refused to participate, and 2 were unable to consent). These 84 patients were randomly allocated to the esketamine group (n = 42) or the normal saline group (n = 42). All randomized patients received the intervention and were included in the final intention-to-treat analysis. Throughout the study and follow-up, no patient was lost to follow-up or withdrew due to a protocol deviation (Figure 1). The baseline characteristics did not differ between the groups (Table 1). Furthermore, esketamine-related adverse reactions were not reported in Group K. The incidence of cough reflex in Group K patients was lower than that in Group S ($P < 0.001$). When comparing the

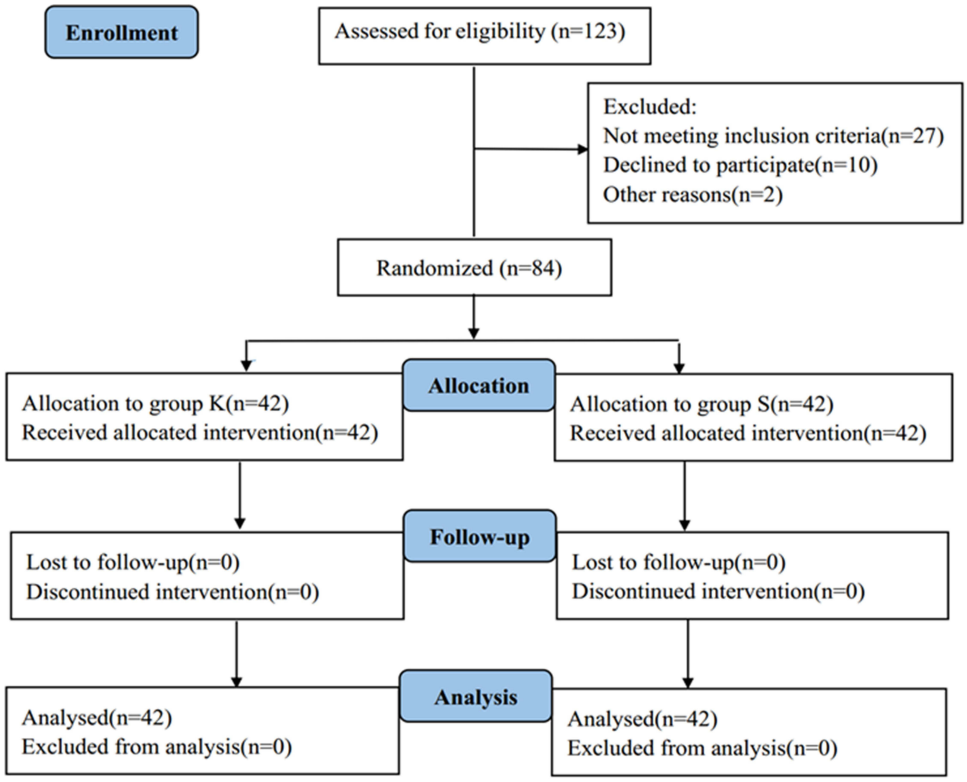

Figure 1 The clinical procedures in the study adhered to the CONSORT flow.

intensity of the cough reflex between the two groups, it was evident that Group K had more patients with milder symptoms. (P<0.001) (Table 2). No difference was detected in the MAP and HR between the groups (Table 3).

Moreover, the Riker Sedation-Agitation Scale scores did not differ between the groups (P > 0.05). The RSS score post-extubation was higher in Group K than in Group S (P = 0.002). As shown in Table 4, compared with Group S, the incidence of POST reported by patients in Group K was lower at 2, 4, 6, 12, and 24 hours following extubation (all P<0.05). At 2, 4, 6, 12, and 24 hours after extubation, the severity of POST reported by patients in Group K was lower than that in Group S (all P<0.05).

Table 1 Patients' Baseline Variables

	Group K (n=42)	**Group S (n=42)**	***P*-value**
Age (years)	51.05±9.44	52.90±8.86	0.355
Sex, male/female (n)	18/24	19/23	0.826
BMI (kg/m^2)	23.60±2.66	24.72±2.80	0.063
ASA grade (n,%)			0.239
I	1 (2.4)	0 (0)	
II	36 (85.7)	34 (81.0)	
III	5 (11.9)	8 (19.0)	
Duration of anesthesia (min)	132.69±38.93	144.74±41.33	0.173
Duration of surgery (min)	99.71±36.47	111.79±41.03	0.158

Notes: Values are expressed as numbers (proportions) or mean ± standard deviation.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; Group K, esketamine nebulized inhalation group; Group S, normal saline nebulized inhalation group.

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Table 2 Incidence and Grade of Cough Reflex During Extubation

	GroupK (n=42)	GroupS (n=42)	*P*-value
Incidence of cough reflex, n (%)	13 (31.0)	30 (71.4)	<0.001*
The intensity of cough reflex, n (%)			<0.001*
Grade 0	29 (69.0)	12 (28.6)	
Grade 1	7 (16.7)	11 (26.1)	
Grade 2	4 (9.5)	12 (28.6)	
Grade 3	2 (4.8)	7 (16.7)	

Notes: Values are expressed as numbers (proportions). *Statistically significant. Cough reflex intensity was evaluated during the recovery period from the time of awareness to 5 min following extubation: 0, no cough; 1, minimal (single) cough; 2, moderate (≤5 s) cough; and 3, severe (>5 s) cough (bucking).
Abbreviations: Group K, esketamine nebulized inhalation group; Group S, normal saline nebulized inhalation group.

Table 3 Change in MAP and HR Before and After Treatment

Variables	Group K (n=42)	Group S (n=42)	*P*-value
MAP (mmHg)			
T0	96.55±13.69	98.62±13.79	0.346
T1	98.71±13.31	98.21±13.41	0.864
T2	85.14±10.07	81.81±12.10	0.174
T3	80.64±11.56	81.00±11.44	0.887
T4	84.19±12.33	88.07±11.16	0.134
T5	83.38±11.43	86.29±9.39	0.207
T6	86.81±7.86	88.93±9.32	0.263
HR (beats/min)			
T0	76.93±11.63	79.83±11.99	0.263
T1	72.81±10.80	73.10±12.93	0.913
T2	64.90±10.40	64.12±13.34	0.764
T3	70.62±9.98	70.74±10.27	0.957
T4	77.17±10.66	78.93±12.15	0.482
T5	73.00±8.94	74.98±11.70	0.387
T6	72.76±9.87	75.50±12.47	0.268

Note: Values are expressed as mean±standard deviation.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; T0, before nebulized inhalation; T1, at the end of nebulized inhalation, T2, after the completion of anesthesia induction; T3, upon PACU admission; T4, immediately after extubation; T5, 10 min after extubation; T6, and discharged from the PACU; Group K, esketamine nebulized inhalation group; Group S, normal saline nebulized inhalation group.

Discussion

This study demonstrated that preoperative esketamine nebulized inhalation effectively alleviated cough reflex in extubation of surgical patients and did not cause adverse reactions. It also reduced the incidence and severity of POST.

Among the surgical population, the incidence of cough reflex during extubation ranges from 40% to 96%, which can cause intense discomfort to patients and may lead to serious adverse effects,[4,8] particularly in patients who are susceptible to complications from elevated intracranial or intraocular pressure. The cough reflex can be triggered by mechanical or chemical stimuli that activate sensory receptors in the respiratory tract.[32] Numerous studies have investigated strategies to mitigate the cough reflex during the postoperative extubation period. However, each approach has its unique benefits and drawbacks. Research indicated that a low dose of dexmedetomidine did not adequately suppress the

Table 4 Incidence and Severity of Postoperative Sore Throat (POST)

	GroupK (n=42)	GroupS (n=42)	χ2/Z	*P*-value
POST (n,%)				
0h	8 (19.0)	14 (33.3)	2.217	0.136
2h	7 (16.7)	20 (47.6)	9.224	0.002*
4h	7 (16.7)	18 (42.9)	6.891	0.009*
6h	6 (14.3)	16 (38.1)	6.158	0.013*
12h	3 (7.1)	12 (28.6)	6.572	0.010*
24h	2 (4.8)	8 (19.0)	4.086	0.043*
Severity of POST				
0h	0 (0, 0)	0 (0, 1)	−1.458	0.145
2h	0 (0, 0)	0 (0, 1)	−3.140	0.002*
4h	0 (0, 0)	0 (0, 1)	−2.721	0.007*
6h	0 (0, 0)	0 (0, 1)	−2.537	0.011*
12h	0 (0, 0)	0 (0, 1)	−2.500	0.012*
24h	0 (0, 0)	0 (0, 0)	−2.024	0.043*

Notes: Values are expressed as numbers (proportions), and median (interquartile). *Statistically significant. POST was scored using a numeric rating scale ranging from 0 (no sore throat) to 10 (worst imaginable pain).
Abbreviations: Group K, esketamine nebulized inhalation group; Group S, normal saline nebulized inhalation group; POST, postoperative sore throat.

cough reflex during extubation after surgery,[33] while doses over 0.5 μg/kg led to a notably longer extubation period.[34] Intravenous remifentanil can reduce the incidence of cough reflex during extubation, but it may lead to prolonged recovery time and extubation time.[35] The protective effect of topically applied lidocaine gel may be counteracted by the potential adverse effects of additives or preservatives contained in the formulation.[36] In addition, research showed that 0.5 mg/kg of ketamine could decrease the incidence of cough reflex during extubation for patients receiving laparoscopic surgery,[37] but ketamine can increase sympathetic activity, nausea and vomiting, and may lead to psychotomimetic reactions.[38] Esketamine, the right-handed isomer of ketamine, which is a noncompetitive NMDA receptor blocker, has been newly introduced in China. Esketamine shares its mechanism of action with ketamine, yet it exhibits a stronger affinity for NMDA receptors and minimal side effects. Chen et al found that a subanesthetic dose of esketamine lowered the EC50 of remifentanil to inhibit the cough reflex during extubation.[39]

Esketamine given intravenously has been noted to produce unwanted effects like psychotomimetic reactions,[40] vivid dreaming, and elevated blood pressure.[30] Nebulized inhalation of ketamine represents a new route for administering the substance.[20] This route allows quick absorption, fast onset of action, and high bioavailability.[25] Up to now, no research has observed the potential effect of esketamine nebulized inhalation.

During the process of designing this experiment, no relevant studies on esketamine nebulized inhalation and cough reflex during extubation are available in the existing literature. In our initial testing phase, we assessed two concentration gradients and observed that a 75 mg dose of nebulized esketamine resulted in marked hypertension. Therefore, 50mg of esketamine was used in this study. Reported side effects of esketamine include fluctuations in elevated hemodynamics,[30] and psychomimetic reactions.[40] In this study, no differences in the MAP and HR were observed between the groups at each time point (Table 3), and no associated psychiatric adverse effects occurred during the postoperative follow-up. Therefore, the intervention measures adopted in this study were considered to be safe.

Current studies suggest that esketamine exerts different effects on receptors and channels.[30] The effectiveness of preoperative esketamine nebulized inhalation in reducing cough reflex at extubation can be explained by the following mechanisms: First, it reduces the sensitivity of airway reflexes by inhibiting central sensitization and neurotransmitter release.[39,41] Second, preoperative nebulized inhalation enables the drug to directly act on the airway mucosa to form an effective barrier and may inhibit cough reflex triggered by mechanical stimuli through local anesthetic effects. Third,

esketamine can also directly act on airway smooth muscle to dilate bronchioles through voltage-dependent L-type calcium channels.[42] Further studies are warranted to evaluate the specific mechanisms constituting the basis for the esketamine nebulized inhalation effect against the cough reflex.

In the present study, the RSS score post-extubation was higher in the esketamine group than in the normal saline group. This could be explained by the analgesic, sedative, and cough-suppressant effects of esketamine, which increased the patient's threshold for adverse stimuli. However, the Riker Sedation-Agitation Scale scores were similar between groups.

POST is a common issue following general anesthesia during the postoperative phase.[43] It can provoke significant postoperative morbidity and patient dissatisfaction. The mechanism of POST may be related to the pressure of an endotracheal tube on a tracheal wall, causing airway inflammation, tracheal mucosal traumatization, vocal cord hematoma, mucosal dehydration, or laryngeal edema.[44,45] Therefore, esketamine nebulized inhalation can alleviate local inflammation and exert peripheral analgesic effects, reducing the incidence of POST and postoperative pain scores.[43,46,47]

This study has several limitations. First, we did not evaluate the effect of other doses of esketamine on the incidence of cough reflex during extubation. Further studies are warranted to outline the optimal clinically effective dose for alleviating cough reflex during extubation. Second, as ketamine has been gradually replaced by esketamine in China,[48] no ketamine treatment group was established in this study. Finally, this research was carried out at a single center. Further studies at different institutions are warranted to evaluate the effect of esketamine nebulized inhalation on cough reflex during extubation.

Conclusion

This study demonstrates that preoperative esketamine nebulized inhalation is an effective and safe option for reducing the incidence and intensity of cough reflex during tracheal extubation.

Data Sharing Statement

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

Ethics Approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2024-03-99) and registered with the Chinese Clinical Trial Registry (ChiCTR2400086812). All patients provided written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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