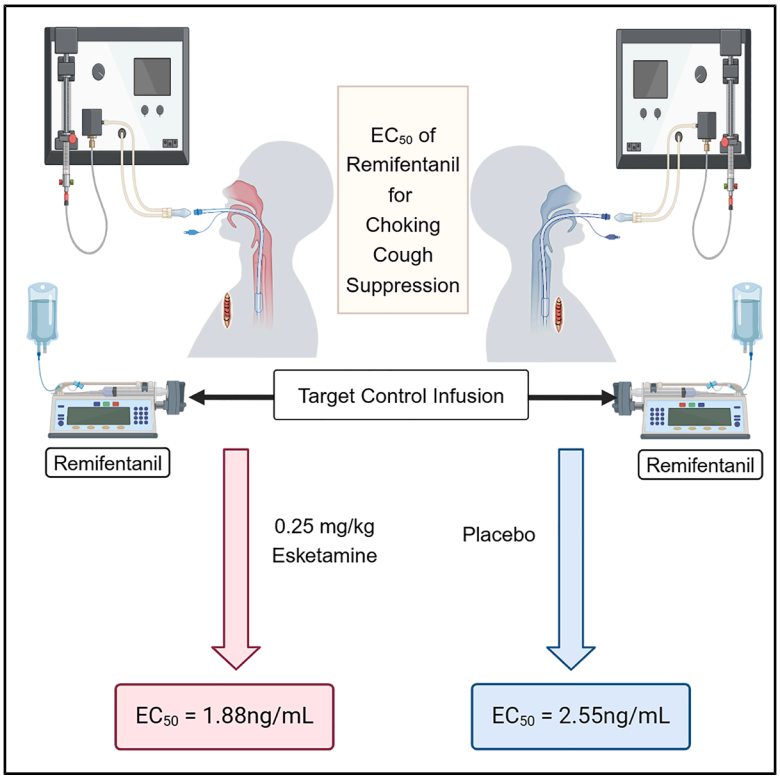
iScience

Article

Effect of esketamine on the EC_{50} of remifentanil for suppression of choking cough during extubation

Graphical abstract



Highlights

- Esketamine can reduce the concentration of remifentanil for inhibiting extubation cough
- Intraoperative esketamine administration is effective in reducing early postoperative pain
- Low doses of esketamine do not significantly impact extubation time or adverse reactions

Authors

Shouyi Chen, Liurong Lin, Qian Zhou, Lanying Lin

Correspondence

659482712@qq.com (Q.Z.), linlanying@163.com (L.L.)

In brief

Health sciences; Medicine; Medical specialty; Anesthesiology

Chen et al., 2025, iScience 28, 112392
May 16, 2025
https://doi.org/10.1016/j.isci.2025.112392

CellPress

iScience

CellPress
OPEN ACCESS

Article

Effect of esketamine on the EC_{50} of remifentanil for suppression of choking cough during extubation

Shouyi Chen,[1,2,3] Liurong Lin,[1,2,3] Qian Zhou,[1,2,*] and Lanying Lin[1,2,4,*]
[1]Department of Anesthesiology, Anesthesiology Research Institute, The First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian 350005, China
[2]Department of Anesthesiology, National Regional Medical Center, Binhai Campus of The First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian 350212, China
[3]These authors contributed equally
[4]Lead contact
*Correspondence: 659482712@qq.com (Q.Z.), linlanying@163.com (L.L.)
https://doi.org/10.1016/j.isci.2025.112392

SUMMARY

Choking cough during awakening from anesthesia is common (15%–94%) and can cause severe discomfort and complications, especially in neck surgery. This study compared the median effective concentration (EC_{50}) of remifentanil combined with esketamine versus remifentanil alone for suppressing cough during extubation in male patients undergoing anterior cervical spine surgery. Group E received 0.25 mg/kg esketamine intravenously 30 min before surgery ended, while group D received a placebo. We observed that the EC_{50} values were 1.88 ng/mL for group E and 2.55 ng/mL for group D. No significant differences were observed in intraoperative hemodynamics or extubation time. Additionally, group E had lower postoperative pain scores at 2 and 24 h. Findings suggest that combining esketamine with remifentanil reduces the EC_{50} for cough suppression and effectively lowers early postoperative pain, providing reference for perioperative safety and improvement of prognosis in patients undergoing anterior cervical surgery.

INTRODUCTION

The incidence of choking cough during awakening from general anesthesia ranges from 15% to 94%,[1] which causes intense discomfort to patients and can lead to serious adverse reactions.[2] Serious complications, such as postoperative incision hematoma, secondary surgery, and cardiac arrest caused by postextubation choking cough have a high incidence in neck surgery, making prevention of awakening choking cough in neck surgery particularly important.[3] Numerous studies have been conducted so far on methods to prevent or reduce choking cough during awakening, such as extubation under deep anesthesia, use of alfentanil, remifentanil, dexmedetomidine, ketamine, intrathecal injection of lidocaine, or intravenous lidocaine.[4–8]

Choking cough during extubation during general anesthesia for anterior approach cervical spine surgery not only causes hemodynamic fluctuation but also may cause postoperative incision cracking or even postoperative hematoma, and in severe cases, may compress the trachea and lead to asphyxiation. Remifentanil can prevent or reduce choking cough during the recovery period and reduce complications, and it has the best effect in alleviating severe choking cough during extubation compared with other drugs.[9] Remifentanil, on the other hand, can provide a more accurate and stable blood concentration through target-controlled infusion (TCI) mode for more effective and safe suppression of coughing.[10] Esketamine, as an N-methyl-D-aspartic acid (NMDA) receptor antagonist, can reduce the cough reflex and its induced bronchoconstriction by inhibiting the NMDA receptor.[11] Compared with other drugs, esketamine also reduces pain hypersensitivity caused by remifentanil by inhibiting NMDA receptors in order to reduce postoperative pain and opioid consumption.[12] In addition, studies have found that the respiratory rate and tidal volume recover faster and better after perioperative application of esketamine, and the use of opioids is reduced, thus reducing complications and improving the quality of rehabilitation of patients.[13]

Soh S et al. found gender differences in median effective concentration (EC_{50}) of remifentanil for choking cough suppression during awakening, and the EC_{50} value of remifentanil during thyroidectomy extubation was significantly lower in females than in males (1.23 ng/mL in females and 2.43 ng/mL in males).[14] Opioids bind better to and receptors in the brainstem and suppress the choking cough reflex in female patients during awakening from general anesthesia.[15] A retrospective study found that men were at higher risk of infection, hematoma, and adverse cardiopulmonary events after anterior approach cervical spine surgery.[16] Therefore, single-sex male patients were selected as research objects in this study. In this study, we investigated the effect of esketamine on the choking cough response to remifentanil by comparing the EC_{50} of remifentanil combined with esketamine intraoperatively with that of remifentanil alone to suppress extubation choking cough in male patients undergoing anterior approach cervical spine surgery. Meanwhile, the effects of subanesthetic dose of esketamine on patients' postoperative

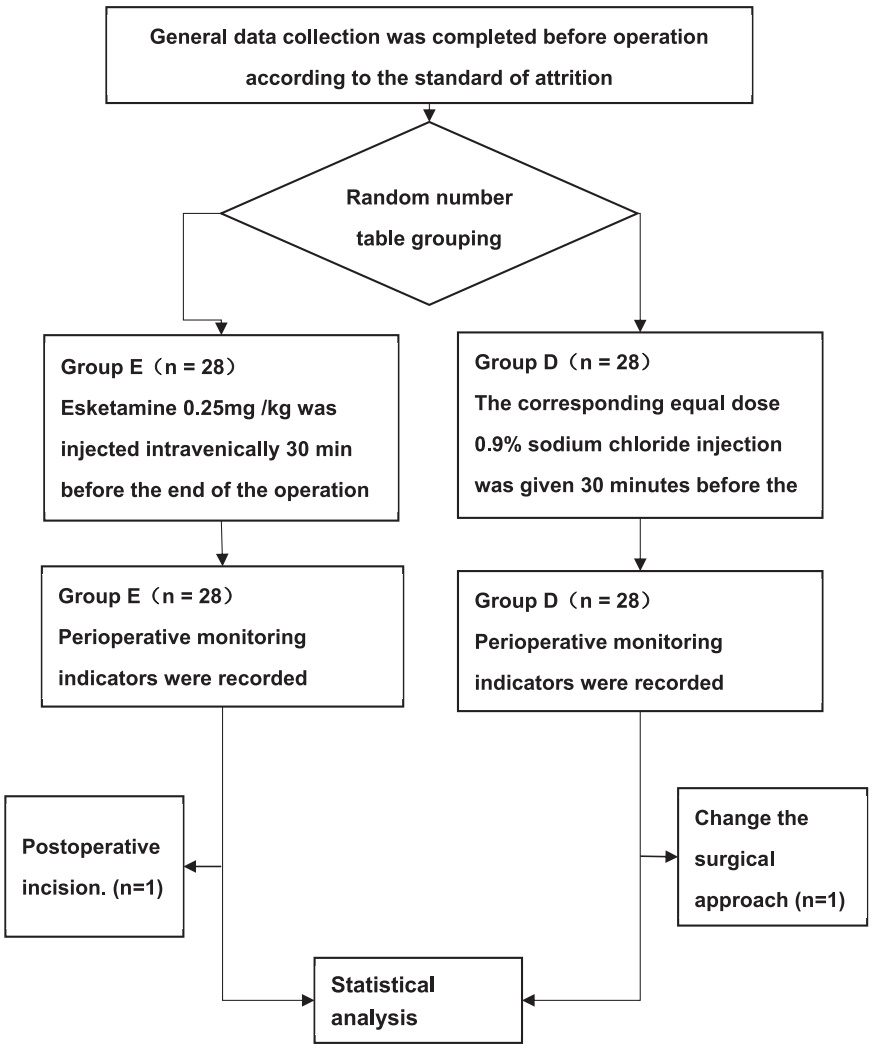


Figure 1. Flow diagram showing the enrollment of patients

acute pain and quality of recovery were investigated to provide reference for maintaining perioperative safety and improving prognosis of anterior approach cervical spine surgery patients.

RESULTS

Analysis of choking cough reaction

During the period from June 2023 to January 2024, a total of 56 patients were recruited in two groups, in which one case of postoperative incision infection reoperation in group E, and one case of changing to posterior cervical spine surgery in group D were excluded, and finally 27 cases in each of group E and group D were included all of them completed the study process and statistical analysis was completed. (Figure 1). The general information of the two groups was distributed in a balanced manner, and none of the differences were statistically significant. (Table 1).

The effector chamber concentrations of remifentanil to suppress the choking cough response in both groups were determined using the modified Dixon sequential method as shown in Figure 2. Twenty-seven study subjects were included in each of the two groups. In group E, 13 patients had a positive choking cough response during extubation, and the lowest remifentanil effector compartment concentration was 1.6 ng/mL, with a total of 6 negative/positive turning points; in group D, 15 patients had a positive choking cough response during extubation, and the lowest remifentanil effector compartment concentration was 2.0 ng/mL, with a total of 8 negative/positive turning points, which satisfied the sample size requirement of the modified Dixon sequential method sample size requirements.

The probabilistic unit regression model for the suppression of choking cough response during extubation by remifentanil in the two groups was analyzed by Probit probabilistic unit regression analysis as Probit(P)E = −12.768 + 6.792 remifentanil concentration, Probit(P)D = −17.345 + 6.792 remifentanil concentration, and $p > 0.05$ for the goodness-of-fit test of the regression model, indicating that the whole regression model fitted the data well, indicating that the entire regression model fits the data well.

According to this regression model, the EC_{50} of remifentanil for suppressing the choking cough response during extubation in group E in this study was 1.880 (95% confidence interval [CI] 1.782–1.973) ng/mL, and the EC_{95} was 2.122 (95% CI 2.017–2.379) ng/mL, and in group D, the EC_{50} was 2.554 (95% CI 2.458–2.656) ng/mL and EC_{95} was 2.796 (95% CI 2.685–3.071) ng/mL, and the difference in EC_{50} between the two groups was 0.674 (95% CI 0.223–1.989) ng/mL as estimated by the relative median intensity, whose 95% confidence interval did not include 0, indicating that the difference was statistically significant. The volume-efficacy relationship curves of remifentanil for inhibiting the extubation choking cough response in the two groups were shown in Figure 3.

Analysis of relevant characteristics in extubation period

Repeated-measures ANOVA analysis of PaO_2 and $PaCO_2$ in arterial blood gas analysis of the two groups showed that overall there was no significant difference between the two groups in the perioperative period ($p > 0.05$), and that $PaCO_2$ continued to rise in both groups from T_0 to T_4. At the moment of T_4 $PaCO_2$ was lower in group E than in group D. The difference was statistically significant ($p < 0.05$) (Figure 4). Figure 5 showed a schematic diagram of the trend of mean arterial pressure and heart rate in the

Table 1. Comparison of preoperative basic information and medical history between the two groups

	Group E (n = 27)	Group D (n = 27)	p
Year(y)	53.22 ± 7.54	55.81 ± 6.36	0.178
Height (cm)	168.26 ± 4.90	168.44 ± 5.55	0.897
Weight (kg)	69.37 ± 10.24	66.81 ± 10.07	0.359
BMI(kg/m^2)	24.27 ± 2.95	23.55 ± 2.98	0.375
ASA (I/II)	4/23	5/22	0.971
Recent smoking history	14 (51.85%)	13 (48.15%)	0.785
Hypertension	4 (14.81%)	6 (22.22%)	0.484
Diabetes	4 (14.81%)	5 (18.52%)	0.715
Operation time (min)	105 (70,160)	90 (70,120)	0.703
Anesthesia time (min)	120 (80,175)	105 (80,135)	0.678
The total dose of remifentanil (μg)	900 (613,1348)	792 (648,1024)	0.382

Data are presented as mean (standard deviation), median (interquartile range, IQR) or n [%].
BMI, Body mass index; ASA, American society of anesthesiologists.

two groups. According to the results of repeated-measures ANOVA, the trend of Mean Arterial Pressure (MAP) and Heart Rate (HR) changes in the two groups during the perioperative period was approximately the same ($p > 0.05$). A two-by-two comparison showed that MAP and HR were significantly lower at the moment of T_1 than at other time points in both groups ($p < 0.05$), and the differences between the moments of T_0, T_2, T_3, and T_4 were not statistically significant.

Postoperative recovery quality and adverse reaction analysis

Postoperative numerical rating scale (NRS) scores were statistically analyzed using generalized estimating equations. Overall it can be concluded that the difference in NRS scores between the two groups was statistically significant ($p < 0.05$). Comparison between the two groups showed that the NRS scores of the two groups continued to decrease from 2 h to 48 h. The NRS scores of group E were significantly lower than those of group D at 2 h and 24 h postoperatively, with a statistically significant difference ($p < 0.05$), and the NRS scores of the two groups at 48 h postoperatively were approximately similar. Postoperative remedial analgesic drugs were also analyzed, and one case of remedial analgesic drugs was used in group E, while three cases were in group D. The difference in postoperative remedial analgesic drugs between the two groups was not statistically significant ($p = 0.603$). (Table 2)

The differences in $PetCO_2$ and respiratory rate at the immediate moment of extubation between the two groups were statistically significant ($p < 0.05$). In addition, only two patients in group D showed post-extubation respiratory depression, and there was no significant difference in the incidence of respiratory-related adverse events after extubation between the two groups. There was no statistically significant difference in the extubation choking cough score, Ramsey score, and postoperative sore throat (POST) score at 30 min after extubation, the amount of drainage in the drainage bag at 12 h, 24 h, and 48 h postoperatively, the length of drainage tube placement, the length of postoperative hospitalization, and the occurrence of adverse events between the two groups. Postoperative nightmare occurred in 1 person in group E and nausea and vomiting in 3 persons in group D. Postoperative patient health questionnaire 9(PHQ-9) scores were lower than preoperative in group E and higher than preoperative in group D, but there was no significant difference. (Table 3)

DISCUSSION

In this study, we found that compared with remifentanil infusion alone, the combined application of esketamine significantly reduced the EC_{50} and EC_{95} of remifentanil in suppressing the choking cough response during extubation, and the difference of EC_{50} between the two groups was 0.674 (95% CI 0.223–1.989) ng/mL. The NRS scores in the esketamine group at 2 h and 24 h postoperatively were significantly lower than those in the control group and the difference of extubation. The differences in immediate $PetCO_2$ and respiratory rate were statistically significant. There was no statistically significant difference in the incidence of respiratory-related adverse events, quality of postoperative recovery, and occurrence of adverse reactions between the two groups after extubation.

The cough reflex can be activated using glutamate via N-methyl-D-aspartic acid (NMDA) and non-NMDA receptors,[17] and tracheal tubes, secretions stimulate respiratory cough receptors during awakening from anesthesia, which in turn initiates the cough response via NMDA receptors.[18,19] In this study, we found that the application of a subanesthetic dose of esketamine reduced the EC_{50} of remifentanil to inhibit the choking cough response during extubation, did not affect the extubation time, and had a low incidence of postoperative adverse effects. Demir significantly reduced the occurrence of choking cough during extubation by injecting 0.5 mg/kg of ketamine before the end of the operation, but the extubation time in the ketamine group was longer than that in the control group.[20] Side effects of ketamine include nightmares, hallucinations, confusion, and hyperexcitability, which were dose related.[21] Esketamine was the pure dextro isomer of ketamine, with an affinity for NMDA receptors 2–3 times higher than that of ketamine, and it had a significantly shorter postanesthetic awakening time and oriented recovery time, fewer psychiatric side effects, and a lower incidence of adverse effects in the subanesthetic dosage range (0.15–0.25 mg/kg).[18,22] Esketamine takes effect 1–2 min after intravenous injection, with a distribution half-life of 23 min and an elimination half-life of 125–180 min.[23] The results of this study showed no statistical difference in eye opening time and extubation time in group E compared with the control group, suggesting that intravenous injection of 0.25 mg/kg of esketamine 30 min before the end of the operation had no significant effect on the patient's awakening time, which provides a dosing reference for the use of esketamine.

Remifentanil was an ultrashort-acting opioid,[19] and its antitussive effect prevented or reduced choking cough during the awakening period, and it was the most effective in relieving severe choking cough during the extubation period compared with other drugs.[24] However, the incidence of adverse effects,

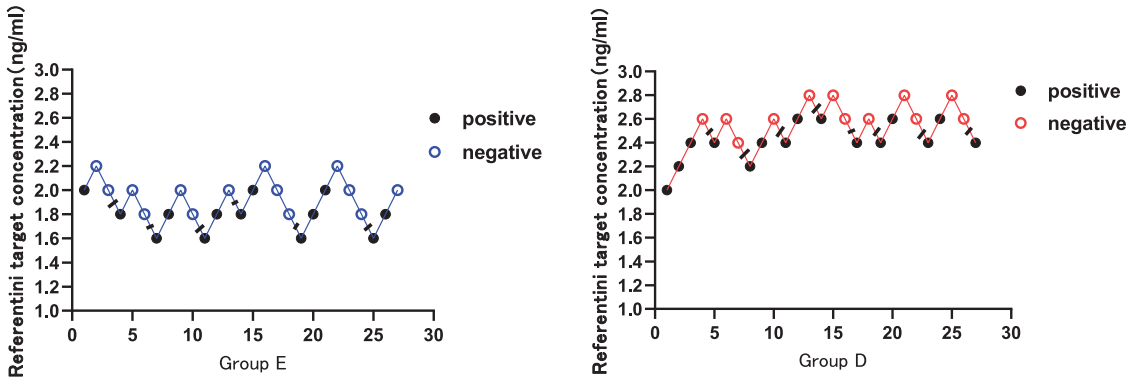


Figure 2. Effect-site concentration of remifentanil by Dixon's method of the two groups

The positive and negative choking cough reactions are represented as open (○) and closed circles (●), respectively.

such as respiratory depression, nausea and vomiting, muscle stiffness, itching, or delayed awakening was also increased with increasing dose.[25] The TCI effector compartment concentrations of remifentanil to suppress the choking cough reflex recommended in previous literature varied and ranged from 1.5–2.9 ng/mL.[14,25–27] When remifentanil effector compartment target concentration of 2 ng/mL was maintained during the extubation period, it was effective in suppressing the incidence and severity of cough during extubation in both propofol-remifentanil anesthesia modality and sevoflurane-remifentanil anesthesia modality, with no significant difference between the two groups,[28] which was similar to the EC_{95} value of remifentanil that suppressed the choking cough response during extubation in propofol-remifentanil anesthesia modality.[29]

There was no significant difference in the incidence of respiratory-related adverse events after extubation between the two groups, but we found that two patients in group D had postextubation respiratory depression. This study showed a difference of 0.6–0.7 ng/mL between remifentanil EC_{50} and EC_{95} between the two groups. Using high concentrations of remifentanil to prevent coughing may be impractical, as remifentanil during recovery may increase hypnosis and respiratory depression. According to previous studies, the incidence of hypoventilation caused by

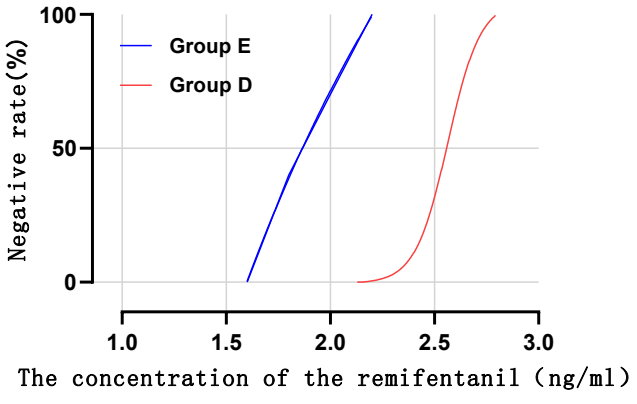


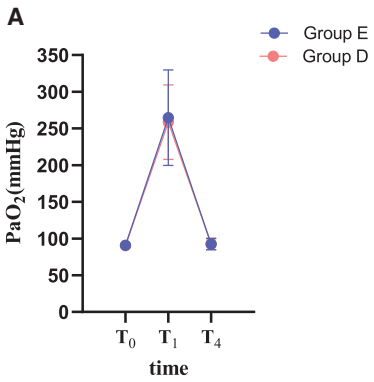
Figure 3. Schematic diagram of dose-effect curves of remifentanil for preventing choking cough reaction of the two groups

3.0 ng/mL remifentanil infusion during recovery is higher than that caused by 2.6 ng/mL or lower remifentanil infusion of 2.6 ng/mL, and the extubation time during recovery is longer.[30] These results suggest that the combination of esketamine and remifentanil for the prevention of waking cough is feasible in a clinical setting.

When remifentanil was used alone in this study, the EC_{50} of remifentanil to inhibit extubation choking cough was 2.554 ng/mL, which was slightly higher compared with 2.43 ng/mL in the study of Soh S et al.[14] in the thyroidectomy study, probably because the need to wear a neck brace in the postoperative period of cervical spine surgery increased the mechanical stimulation of the pharynx coming into contact with the tracheal tube during the awakening period compared with thyroidectomy, which increased the choking cough probability of occurrence. Previous studies found that esketamine gargle was effective in reducing post-tracheal intubation sore throat by acting on oral and upper respiratory mucosal opioid receptors and inhibiting NMDA receptors *in vivo*, which lasted for at least 7 days postoperatively, and no adverse effects associated with esketamine had been found.[31] No significant difference was found between the two groups of postoperative sore throat in this study, which may be due to the small sample size of esketamine.

The difference between the two groups in this study was not statistically significant in terms of total intraoperative remifentanil dose, but $PetCO_2$ at the moment of extubation and $PaCO_2$ 3 min after extubation were lower in patients of group E relative to the control group. The subanesthetic dose of esketamine was effective in reversing remifentanil-induced respiratory depression, probably because esketamine blocks NMDA receptors and improves the sensitivity of chemoreceptors to carbon dioxide *in vivo*,[32] and also improves the efficiency of monoamine neurotransmitter delivery in respiratory activity due to its synergistic effect on catecholamines.[33] The recovery of respiratory rate was better in group E at the immediate moment of extubation, suggesting that the coadministration of esketamine helps to reduce the use of opioids during extubation, accelerates the recovery of respiratory function during the awakening period, and reduces complications.

Esketamine also helped to reduce the patients' postoperative pain. NRS scores continued to decrease from 2 h to 48 h



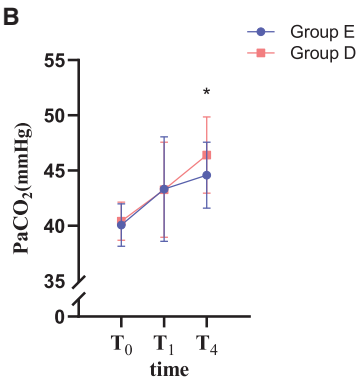
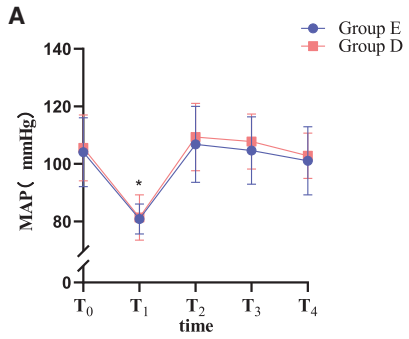


Figure 4. Respiratory function index trends of the two groups

Data are represented as mean ± SEM. T_0: entry into the operating room, T_1: 30 min before the end of surgery, T_4: 3 min after extubation. (A) indicates the trend diagram of PaO_2 of the two groups, (B) indicates the trend diagram of $PaCO_2$ of the two groups. * represents that $PaCO_2$ in group E was lower than that in group D at T_4, and the difference was statistically significant ($p < 0.05$).

postoperatively in both groups, but the NRS scores in group E were significantly lower than those in group D at both 2 h and 24 h postoperatively. Postoperative pain in perioperative patients was mainly affected by various factors such as central sensitization, surgical injury and inflammatory factor release,[34] in addition to nociceptive hypersensitivity induced by anesthesia maintenance with remifentanil.[35] Esketamine can reduce pain by inhibiting NMDA receptor-mediated pain sensitization and central sensitization, and can reduce remifentanil-induced nociceptive hypersensitivity by interacting with opioid receptors.[12] Shen J et al. used 0.25 mg/kg of esketamine to effectively reduce pain 24 h after abdominal surgery, reduce the dosage of opioids without any significant adverse effects, and improve the quality of recovery.[36] In this study, the esketamine group reduced patients' pain at 2 h and 24 h after surgery, but there was no statistically significant difference between the NRS scores and the use of remedial analgesic drugs between the two groups at 48 h after surgery, which may be due to the fact that anterior cervical spine approach surgery is less traumatic, postoperative pain was less severe and would not be aggravated by exercise, and flurbiprofenac was routinely injected intravenously for two days after surgery to provide postoperative analgesia, so that patients of the two groups showed moderately severe pain (NRS) and pain in the first two days after surgery. The number of patients with moderate-to-severe pain (NRS score more than or equal to 4) was very small, and only three patients in the control group required remedial analgesic medication, so the analgesic effect of esketamine on the 48 h postoperative period in this study was not significant. Nevertheless, intraoperative infusion of esketamine may also help to reduce postoperative pain scores and improve the quality of patients' postoperative recovery, but further studies were needed.

Postoperative cervical spine surgery in patients with anterior approach to the cervical spine restricts neck movement due to the wearing of a neck brace, which caused great discomfort to the patients and may produce negative emotions, affecting the postoperative recovery. The PHQ-9 scores of group E were lower than those of the preoperative period, which suggested that esketamine has some improvement in the postoperative depression of the patients, but there was no significant difference, probably because the study subjects were middle-aged and young men, and anterior approach to the cervical spine surgery had a small incision with low incidence of moderate-to-severe pain and a high incidence of postoperative depression. The incidence of moderate to severe pain was low, and postoperative depression was associated with factors including age, gender, postoperative pain, and anxiety. The NMDA receptor antagonists ketamine or esketamine increase free glutamate, decrease serum inflammatory factor levels, and increase the expression of brain-derived neurotrophic factor, thus exerting an antidepressant effect, and the most commonly used dose to exert an antidepressant effect was intravenous ketamine at 0.5 mg/kg and the mood-improving effect lasts for about a week.[37] While increasing the frequency of intravenous administration prolongs the antidepressant effect, it also increased the risk of ketamine psychomimetic side effects.[38]



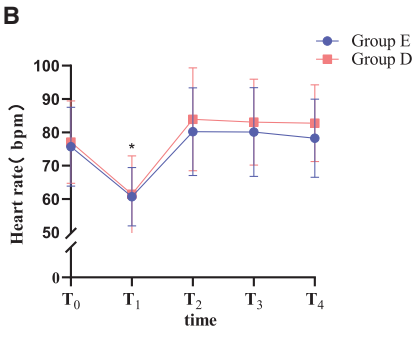


Figure 5. Intraoperative hemodynamic trends of the two groups

Data are represented as mean ± SEM. T_0: entry into the operating room, T_1: 30 min before the end of surgery, T_2: extubation, T_3: 1 min after extubation, T_4: 3 min after extubation. A indicates the trend diagram of MAP of the two groups, B indicates the trend diagram of HR of the two groups. * means that the MAP and HR at T_1 were significantly lower than those at other time points ($p < 0.05$).

Table 2. Postoperative NRS scores between two groups

	Group E (n = 27)	Group D (n = 27)	p
2 h after surgery	3 (3,4)[a]	4 (4,4)[a]	0.009
24 h after surgery	3 (3,4)[a]	4 (4,4)[a]	0.001
48 h after surgery	3 (2,3)	3 (3,3)	1.000
Group	Wald = 6.944, p = 0.008		
Time	Wald = 319.321, p < 0.001		
Group[a] × Time	Wald = 35.283, p < 0.001		

Data are presented as median (interquartile range, IQR).
NRS, Numerical rating scale.
[a]Represents that the NRS scores of group E at 2 h and 24 h after operation were statistically lower than those of group D (p < 0.05).

There was no significant difference in the incidence of postoperative nausea and vomiting, dizziness, nightmares, and hallucinations in both groups of patients in this study, and nightmares were only observed in one patient in the esketamine group. The psychomimetic side effects of ketamine were positively correlated with its administered dose, and low doses of ketamine can significantly reduce its self-induced psychiatric symptoms.[39] Compared to ketamine, esketamine had a higher clearance rate in the body and a shorter recovery time, resulting in a lower incidence of postoperative psychomimetic side effects.[35] Based on the concept of enhanced recovery after surgery (ERAS), it had been shown that perioperative removal of opioidized anesthesia with esketamine and dexmedetomidine reduces postoperative nausea and vomiting, delayed recovery of gastrointestinal function, and nociceptive hypersensitivity and other adverse effects, but bradycardia and delayed awakening can still be seen among them.[40] Thus, further studies were needed on the dosage and potential benefits of administration of esketamine and dexmedetomidine under the ERAS concept.

Conclusion

Combined use of esketamine(0.25 mg/kg) can reduce the EC_{50} of remifentanil for inhibiting choking cough during extubation in male patients undergoing anterior approach cervical spine surgery, and it can effectively reduce the early postoperative pain, and it can reduce the concentration of remifentanil used during extubation. The effect-site concentration of remifentanil may be adjusted to prevent emergence cough when used in combination with esketamine. Low doses of esketamine do not significantly impact extubation time or cause adverse reactions.

Limitations of the study

This study had some limitations. First, a single dose of esketamine was administered intravenously in this study, and the efficacy may have varied depending on the blood concentration; the optimal dose, blood concentration, and route of administration of esketamine need to be determined. Second, this study used sevoflurane-remifentanil sedation-aspiration combination anesthesia, and the residual concentration of sevoflurane at the time of extubation may affect the cough reflex, which may yield different results if it is maintained with total intravenous anesthesia. Finally, although there were no significant differences in the incidence of postoperative hemodynamics, proposed psychiatric side effects, and PHQ-9 depression scale scores between the two groups, only male patients were selected for this study and the sample size was small, so whether the dose of esketamine used affects patients including females needs to be further investigated.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Lanying Lin (linlanying@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- This paper does not report the original code.
- All data reported in this paper will be shared by the lead contact upon reasonable request.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.
- Data sharing statement: the datasets are available from the lead contact upon reasonable request.

ACKNOWLEDGMENTS

We thank all participants in this study. The graphical abstract is created in BioRender. Chen, S. (2025) https://BioRender.com/undefined.

AUTHOR CONTRIBUTIONS

Shouyi Chen, data collection, manuscript drafting, and editing; Liurong Lin, data collection, analysis, and initial manuscript drafting; Qian Zhou, resource support and preliminary project oversight; Lanying Lin, study design, manuscript drafting, and editing; all of the authors have read and approved the manuscript.

DECLARATION OF INTERESTS

All authors declared no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Study design
  - Inclusion criteria
  - Exclusion criteria
- METHOD DETAILS
  - Randomization and blindness
  - Clinical protocol
  - Outcomes
- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2025.112392.

Table 3. Comparison of extubation indexes between the two groups

	Group E (n = 27)	Group D (n = 27)	p
Eye opening time (min)	13.44 ± 1.91	12.22 ± 2.70	0.060
Extubation time (min)	14.19 ± 1.81	13.13 ± 2.79	0.106
$PetCO_2$ at the immediate moment of extubation (mmHg)	42 (40,43)[a]	44 (42,45)[a]	0.005
Respiratory rate at the immediate moment of extubation (bpm)	13 (12,14)[a]	11 (11,12)[a]	<0.001
Respiratory adverse events	0 (0)	2 (7.41%)	0.471
Extubation cough score			
0	6 (22.22%)	7 (25.93%)	0.949
1	8 (29.63%)	5 (18.52%)	
2	9 (33.33%)	12 (44.44%)	
3	4 (14.81%)	3 (11.11%)	
Ramsey score 30 min after extubation			
1	1 (3.70%)	0 (0)	0.963
2	10 (37.04%)	11 (40.74%)	
3	8 (29.63%)	9 (33.33%)	
4	8 (29.63%)	7 (25.93%)	
POST score 30 min after extubation			
0	16 (59.26%)	11 (40.74%)	0.104
1	9 (33.33%)	10 (37.04%)	
2	2 (7.41%)	5 (18.52%)	
3	0 (0)	1 (3.70%)	
Drainage 12 h after surgery (ml)	20 (10,30)	20 (15,30)	0.828
Drainage 24 h after operation (ml)	20 (10,25)	20 (10,25)	0.440
Drainage 48 h after operation (ml)	10 (5,20)	10 (0,20)	0.772
Drainage tube placement time(h)	68 (62,88)	64 (53,75)	0.722
Length of postoperative stay(h)	103 (85,116)	110 (90,117)	0.640
Postoperative nausea and vomiting	0 (0)	3 (11.11%)	0.235
Dizziness	2 (3.70%)	3 (11.11%)	0.638
Nightmare	1 (3.70%)	0 (0)	0.317
PHQ-9 score the day before surgery	0 (0,2)	0 (0,1)	1.000
PHQ-9 score one week after surgery	0 (0,2)	0 (0,2)	1.000

Data are presented as mean (standard deviation), median (interquartile range, IQR) or n [%].
POST, postoperative sore throat; PHQ-9, patient health questionnaire.
[a]Represents that the difference are statistically significant ($p < 0.05$).

Received: December 1, 2024
Revised: February 4, 2025
Accepted: April 4, 2025
Published: April 8, 2025

REFERENCES

1. Yang, S.S., Wang, N.N., Postonogova, T., Yang, G.J., McGillion, M., Beique, F., and Schricker, T. (2020). Intravenous lidocaine to prevent postoperative airway complications in adults: a systematic review and meta-analysis. Br. J. Anaesth. *124*, 314–323. https://doi.org/10.1016/j.bja.2019.11.033.
2. Irwin, R.S. (2006). Complications of cough: ACCP evidence-based clinical practice guidelines. Chest *129*, 54S–58S. https://doi.org/10.1378/chest.129.1_suppl.54S.
3. Elbers, L.P.B., Squizzato, A., and Gerdes, V.E.A. (2018). Thyroid Disorders and Hemostasis. Semin. Thromb. Hemost. *44*, 676–682. https://doi.org/10.1055/s-0038-1666825.
4. Lee, M.G., Chang, Y.J., Park, J.M., and Park, H.Y. (2011). The clinical effective dose of alfentanil for suppressing cough during emergence from desflurane anesthesia. Korean J. Anesthesiol. *61*, 292–296. https://doi.org/10.4097/kjae.2011.61.4.292.
5. Nath, P., Williams, S., Méndez, L.F.H., Massicotte, N., Girard, F., and Ruel, M. (2018). Alkalinized Lidocaine Preloaded Endotracheal Tube Cuffs Reduce Emergence Cough After Brief Surgery: A Prospective Randomized Trial. Anesth. Analg. *126*, 615–620. https://doi.org/10.1213/ANE.0000000000002647.
6. Clivio, S., Putzu, A., and Tramèr, M.R. (2019). Intravenous Lidocaine for the Prevention of Cough: Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesth. Analg. *129*, 1249–1255. https://doi.org/10.1213/ANE.0000000000003699.
7. Lee, J.S., Choi, S.H., Kang, Y.R., Kim, Y., and Shim, Y.H. (2015). Efficacy of a single dose of dexmedetomidine for cough suppression during anesthetic emergence: a randomized controlled trial. Can. J. Anaesth. *62*, 392–398. https://doi.org/10.1007/s12630-014-0295-6.

8. Chungsamarnyart, Y., Pairart, J., and Munjupong, S. (2022). Comparison of the effects of intravenous propofol and propofol with low-dose ketamine on preventing postextubation cough and laryngospasm among patients awakening from general anaesthesia: A prospective randomised clinical trial. J. Perioper. Pract. *32*, 53–58. https://doi.org/10.1177/1750458920912636.

9. Dogra, S., and Conn, P.J. (2021). Targeting metabotropic glutamate receptors for the treatment of depression and other stress-related disorders. Neuropharmacology *196*, 108687. https://doi.org/10.1016/j.neuropharm.2021.108687.

10. van Hese, L., Theys, T., Absalom, A.R., Rex, S., and Cuypers, E. (2020). Comparison of predicted and real propofol and remifentanil concentrations in plasma and brain tissue during target-controlled infusion: a prospective observational study. Anaesthesia *75*, 1626–1634. https://doi.org/10.1111/anae.15125.

11. Jat, K.R., and Chawla, D. (2012). Ketamine for management of acute exacerbations of asthma in children. Cochrane Database Syst. Rev. *11*, CD009293. https://doi.org/10.1002/14651858.CD009293.pub2.

12. Bornemann-Cimenti, H., Wejbora, M., Michaeli, K., Edler, A., and Sandner-Kiesling, A. (2016). The effects of minimal-dose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial. Minerva Anestesiol. *82*, 1069–1076.

13. Yuan, J., Chen, S., Xie, Y., Wang, Z., Xing, F., Mao, Y., Wang, J., Yang, J., Li, Y., and Fan, X. (2022). Intraoperative Intravenous Infusion of Esmketamine Has Opioid-Sparing Effect and Improves the Quality of Recovery in Patients Undergoing Thoracic Surgery: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Pain Physician *25*, E1389–E1397.

14. Soh, S., Park, W.K., Kang, S.W., Lee, B.R., and Lee, J.R. (2014). Sex differences in remifentanil requirements for preventing cough during anesthetic emergence. Yonsei Med. J. *55*, 807–814. https://doi.org/10.3349/ymj.2014.55.3.807.

15. Kamei, J. (1996). Role of opioidergic and serotonergic mechanisms in cough and antitussives. Pulm. Pharmacol. *9*, 349–356. https://doi.org/10.1006/pulp.1996.0046.

16. Basques, B.A., Hijji, F.Y., Khechen, B., Haws, B.E., Mayo, B.C., Massel, D. H., Louie, P.K., Cardinal, K.L., Guntin, J.A., and Singh, K. (2018). Sex Differences for Anterior Cervical Fusion: Complications and Length of Stay. Spine *43*, 1025–1030. https://doi.org/10.1097/BRS.0000000000002512.

17. Chung, K.F. (2015). NMDA and GABA receptors as potential targets in cough hypersensitivity syndrome. Curr. Opin. Pharmacol. *22*, 29–36. https://doi.org/10.1016/j.coph.2015.03.002.

18. Han, C., Ji, H., Guo, Y., Fei, Y., Wang, C., Yuan, Y., Ruan, Z., and Ma, T. (2023). Effect of Subanesthetic Dose of Esketamine on Perioperative Neurocognitive Disorders in Elderly Undergoing Gastrointestinal Surgery: A Randomized Controlled Trial. Drug Des. Devel. Ther. *17*, 863–873. https://doi.org/10.2147/DDDT.S401161.

19. Beers, R., and Camporesi, E. (2004). Remifentanil update: clinical science and utility. CNS Drugs *18*, 1085–1104. https://doi.org/10.2165/00023210-200418150-00004.

20. Demir, C.Y., and Yuzkat, N. (2018). Prevention of Emergence Agitation with Ketamine in Rhinoplasty. Aesthetic Plast. Surg. *42*, 847–853. https://doi.org/10.1007/s00266-018-1103-4.

21. Quibell, R., Fallon, M., Mihalyo, M., Twycross, R., and Wilcock, A. (2015). Ketamine. J. Pain Symptom Manage. *50*, 268–278. https://doi.org/10.1016/j.jpainsymman.2015.06.002.

22. Wang, J., Huang, J., Yang, S., Cui, C., Ye, L., Wang, S.Y., Yang, G.P., and Pei, Q. (2019). Pharmacokinetics and Safety of Esketamine in Chinese Patients Undergoing Painless Gastroscopy in Comparison with Ketamine: A Randomized, Open-Label Clinical Study. Drug Des. Devel. Ther. *13*, 4135–4144. https://doi.org/10.2147/DDDT.S224553.

23. Zanos, P., Moaddel, R., Morris, P.J., Riggs, L.M., Highland, J.N., Georgiou, P., Pereira, E.F.R., Albuquerque, E.X., Thomas, C.J., Zarate, C.A., Jr., and Gould, T.D. (2018). Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol. Rev. *70*, 621–660. https://doi.org/10.1124/pr.117.015198.

24. Tung, A., Fergusson, N.A., Ng, N., Hu, V., Dormuth, C., and Griesdale, D.E. G. (2020). Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. Br. J. Anaesth. *124*, 480–495. https://doi.org/10.1016/j.bja.2019.12.041.

25. Chang, C.H., Lee, J.W., Choi, J.R., and Shim, Y.H. (2013). Effect-site concentration of remifentanil to prevent cough after laryngomicrosurgery. Laryngoscope *123*, 3105–3109. https://doi.org/10.1002/lary.24199.

26. Cho, H.B., Kim, J.Y., Kim, D.H., Kim, D.W., and Chae, Y.J. (2012). Comparison of the optimal effect-site concentrations of remifentanil for preventing cough during emergence from desflurane or sevoflurane anaesthesia. J. Int. Med. Res. *40*, 174–183. https://doi.org/10.1177/147323001204000118.

27. Yoo, J.Y., Kim, J.Y., Kwak, H.J., Lee, D.C., Kim, G.W., Lee, S.Y., and Chae, Y.J. (2016). Effect-site concentration of remifentanil for preventing cough during emergence in elderly patients undergoing nasal surgery: a comparison with adult patients. Clin. Interv. Aging *11*, 1247–1252. https://doi.org/10.2147/CIA.S108705.

28. Kim, H., Choi, S.H., Choi, Y.S., Lee, J.H., Kim, N.O., and Lee, J.R. (2012). Comparison of the antitussive effect of remifentanil during recovery from propofol and sevoflurane anaesthesia. Anaesthesia *67*, 765–770. https://doi.org/10.1111/j.1365-2044.2012.07136.x.

29. Lee, B., Lee, J.R., and Na, S. (2009). Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol-remifentanil anaesthesia for thyroid surgery. Br. J. Anaesth. *102*, 775–778. https://doi.org/10.1093/bja/aep090.

30. Kim, H.Y., Kim, J.Y., Ahn, S.H., Lee, S.Y., Park, H.Y., and Kwak, H.J. (2018). Predicting effective remifentanil concentration in 95% of patients to prevent emergence cough after laryngomicroscopic surgery. Medicine *97*, e11258. https://doi.org/10.1097/MD.0000000000011258.

31. Liang, J., Liu, J., Qiu, Z., Sun, G., Xiang, P., Hei, Z., and Li, X. (2023). Effect of Esketamine Gargle on Postoperative Sore Throat in Patients Undergoing Double-Lumen Endobronchial Intubation: A Randomised Controlled Trial. Drug Des. Devel. Ther. *17*, 3139–3149. https://doi.org/10.2147/DDDT.S430077.

32. Patrizi, A., Picard, N., Simon, A.J., Gunner, G., Centofante, E., Andrews, N. A., and Fagiolini, M. (2016). Chronic Administration of the N-Methyl-D-Aspartate Receptor Antagonist Ketamine Improves Rett Syndrome Phenotype. Biol. Psychiatr. *79*, 755–764. https://doi.org/10.1016/j.biopsych.2015.08.018.

33. Zhao, H., Cotten, J.F., Long, X., and Feng, H.J. (2017). The effect of atomoxetine, a selective norepinephrine reuptake inhibitor, on respiratory arrest and cardiorespiratory function in the DBA/1 mouse model of SUDEP. Epilepsy Res. *137*, 139–144. https://doi.org/10.1016/j.eplepsyres.2017.08.005.

34. Ferrini, F., Trang, T., Mattioli, T.A.M., Laffray, S., Del'Guidice, T., Lorenzo, L.E., Castonguay, A., Doyon, N., Zhang, W., Godin, A.G., et al. (2013). Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl^- homeostasis. Nat. Neurosci. *16*, 183–192. https://doi.org/10.1038/nn.3295.

35. Joly, V., Richebe, P., Guignard, B., Fletcher, D., Maurette, P., Sessler, D.I., and Chauvin, M. (2005). Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology *103*, 147–155. https://doi.org/10.1097/00000542-200507000-00022.

36. Shen, J., Song, C., Lu, X., Wen, Y., Song, S., Yu, J., and Sun, J. (2022). The effect of low-dose esketamine on pain and post-partum depression after cesarean section: A prospective, randomized, double-blind clinical trial. Front. Psychiatr. *13*, 1038379. https://doi.org/10.3389/fpsyt.2022.1038379.

37. Aan Het Rot, M., Zarate, C.A., Jr., Charney, D.S., and Mathew, S.J. (2012). Ketamine for depression: where do we go from here? Biol. Psychiatr. *72*, 537–547. https://doi.org/10.1016/j.biopsych.2012.05.003.

38. Singh, J.B., Fedgchin, M., Daly, E.J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J.W., Sanacora, G., Shelton, R.C., et al. (2016). A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. Am. J. Psychiatr. *173*, 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037.

39. Himmelseher, S., and Durieux, M.E. (2005). Ketamine for perioperative pain management. Anesthesiology *102*, 211–220. https://doi.org/10.1097/00000542-200501000-00030.

40. Massoth, C., Schwellenbach, J., Saadat-Gilani, K., Weiss, R., Pöpping, D., Küllmar, M., and Wenk, M. (2021). Impact of opioid-free anaesthesia on postoperative nausea, vomiting and pain after gynaecological laparoscopy - A randomised controlled trial. J. Clin. Anesth. *75*, 110437. https://doi.org/10.1016/j.jclinane.2021.110437.

41. Pace, N.L., and Stylianou, M.P. (2007). Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology *107*, 144–152. https://doi.org/10.1097/01.anes.0000267514.42592.2a.

42. Payton, M.E., Greenstone, M.H., and Schenker, N. (2003). Overlapping confidence intervals or standard error intervals: what do they mean in terms of statistical significance? J. Insect Sci. *3*, 34. https://doi.org/10.1093/jis/3.1.34.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Esketamine	Jiangsu Hengrui Medicine Co	230325BL
Remifentanil	China National Pharmaceutical Group Corporation	20230503
Deposited data		
Raw and analyzed data	Lanying Lin	linlanying@163.com
Software and algorithms		
GraphPad Prism	GraphPad	https://www.graphpad.com/
IBM SPSS	IBM	https://www.ibm.com/products/spss-statistics
BioRender	BioRender	https://BioRender.com/undefined.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design

Approved by the Ethics Committee of our hospital (approval number: Fujian Medical University attached a Research Institute of Ethics [2023]389), and registered by the Chinese Clinical Trial Registry (registration number: ChiCTR2300072315). According to the inclusion and exclusion criteria, 56 male patients who underwent elective cervical spine surgery under tracheal intubation general anesthesia in the First Affiliated Hospital of Fujian Medical University from June 2023 to January 2024 were selected and randomly divided into control group (group D) and esketamine group (group E) using random number table method. All patients had signed the informed consent before operation.

Inclusion criteria

(1) ASA grade I to II; (2) Age:18–65 years old; (3) Cervical spine surgery under tracheal intubation and general anesthesia was performed at an selected time; (4) Body mass index (BMI):18–30 kg/m^2; (5) Patients and family members sign informed consent.

Exclusion criteria

(1) History of allergy to the narcotic drugs used in the study; (2) Patients who refuse to cooperate or are mentally ill; (3) Severe obstructive ventilation dysfunction, bronchial asthma, upper respiratory infection; (4) Patients with severe cardiovascular disease and abnormal liver and kidney function; (5) Patients with grade 3 or above hypertension, or at serious risk of increased intracranial pressure or intraocular pressure; (6) Recent history of sedative and analgesic drug abuse. (7) Intraoperative change of the surgical method (possibly changed to posterior approach cervical surgery); (8) Reoperation is required due to postoperative incision infection and other reasons.

METHOD DETAILS

Randomization and blindness

This study was a prospective, double-blind, randomized controlled trial, with a total of 56 patients, 28 in each group. 56 patients were numbered according to the date and time of surgery, and then random numbers were generated in the random number table, in which the even-numbered patients were divided into esketamine group (n_1 = 28) and the odd-numbered patients into the control group (n_2 = 28). Randomized results were generated by a researcher who was not involved in data collection and statistical analysis and stored in an opaque sealed envelope that was unsealed on the day of surgery. The grouping should not be disclosed to the evaluators of observational indicators and the researchers of data analysis.

Clinical protocol

On the day before surgery, patients were visited to confirm the procedure and informed about preoperative fasting and cooperation during extubation. Basic information (age, height, weight, BMI, ASA classification, smoking history, hypertension, diabetes, and PHQ-9 depression score) was collected. In the operating room, patients underwent cardiac monitoring (HR, SpO_2, MAP) and radial artery cannulation. They were preoxygenated with a face mask (5 L/min) for 1–3 min before anesthesia induction with sufentanil,

propofol, and cisatracurium. A reinforced tracheal tube was inserted using a video laryngoscope, and mechanical ventilation was initiated with 50% oxygen, adjusting parameters to maintain $PetCO_2$ at 35–45 mmHg.

Anesthesia was maintained with sevoflurane (0.6–0.8 MAC) and TCI of remifentanil (3.0–5.0 ng/mL). In the esketamine group, 0.25 mg/kg esketamine was administered 30 min before surgery ended, while the control group received normal saline. Blood pressure and heart rate were maintained within 20% of baseline values. In case of intraoperative hypotension or bradycardia, norepinephrine or atropine was given.

Before wound closure, remifentanil concentration was adjusted to 2 ng/mL. After wound suturing, sevoflurane was discontinued, and the fresh gas flow was increased to 6 L/min to flush the airway. Patients were extubated after achieving adequate respiratory function and consciousness, with remifentanil discontinued immediately after.

Patients received flurbiprofen (50 mg IV) twice daily for analgesia. If severe pain occurred, loxoprofen sodium (60 mg) was administered.

Outcomes

The median effective concentration (EC_{50}) of remifentanil to prevent cough in Group E were the primary study outcomes. The secondary outcomes were postoperative NRS pain score and the occurrence of adverse reactions such as incision bleeding or hematoma, respiratory depression, nausea and vomiting, etc. Postoperative monitoring included HR, MAP, SpO_2, $PetCO_2$, and respiratory rate at various time points (T_0–T_4). The severity of coughing during extubation was assessed using the Minogue Rating Scale. Postoperative complications (e.g., respiratory depression, nausea, hallucinations) were recorded, and patients were followed up at one week to assess the PHQ-9 score.

QUANTIFICATION AND STATISTICAL ANALYSIS

In this study, the Dixon sequential method was used to obtain the EC_{50} value of remifentanil required to suppress choking cough during the extubation period. The EC_{50} of remifentanil was defined as the mean at the mid-point of the crossover concentration for each group (i.e., positive-negative). The EC_{50} value of remifentanil were also estimated using isotonic regression method. Obtaining accurate EC_{50} values by the Dixon sequential method required a minimum of 6 negative/positive turning points and 20 patients per group.[41] In a study of thyroidectomy using the Dixon sequential method, the EC_{50} of remifentanil TCI for male patients to suppress choking cough during extubation was 2.43 ng/mL with a standard deviation of 0.21 ng/mL.[14] Considering the similarity of surgical route, incision size, and patient's position in both thyroidectomy and anterior approach cervical spine surgery, in the present study, the groups were divided per The difference in the target concentration of remifentanil effector compartment between two adjacent cases during extubation was set at 0.2 ng/mL. Additionally, the data of the sequential method trial were analyzed by probit probability unit regression analysis, and the EC_{50} and 95% effective concentration (EC_{95}) of remifentanil for suppressing choking cough during extubation were calculated, as well as the 95% CIs. CIs were calculated using a bootstrapping approach. If the EC_{50} and EC_{95} estimates did not overlap at 83% CI and 95% CI, the values were considered to show statistically significant differences.[42]

The SPSS package (version 26.0, IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Measurement data were tested for normality, and those that conformed to normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$)and independent samples t test was used for comparison between two groups. Measures that did not conform to normal distribution were expressed as median and interquartile spacing [M (P_{25}, P_{75})], and comparisons between the two groups were made using a nonparametric test (Mann-Whitney U-test). The composition of count data was expressed as frequency (percentage) [n (%)], and comparisons between groups were made using the chi-square test or Fisher's exact probability method. NRS scores were analyzed by repeated measures ANOVA or generalized estimating equations. $p < 0.05$ indicated that the difference was statistically significant.

ADDITIONAL RESOURCES

This study was registered on www.chictr.org.cn before first patient enrollment (registration number: ChiCTR2300072315).

The graphical abstract is created in BioRender. Chen, S. (2025) https://BioRender.com/undefined.