Therapeutics and Clinical Risk Management Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Pretreatment with Esketamine Reduces Etomidate-Induced Myoclonus During the Induction of Anesthesia: A Randomized Controlled Trial

Jiang Wang, Mengmeng Zhu, Yuanyuan Cao, Lei Zhang, Lijian Chen

Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, People's Republic of China

Correspondence: Lijian Chen, Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei, 230022, People's Republic of China, Tel +86 13966699467, Email chenlijian77@126.com

Background: Myoclonus is a common problem during induction of anesthesia with etomidate. A variety of agents, including opioids and lidocaine, reduced the incidence of myoclonus. However, there is no reported literature evaluating the effect of esketamine pretreatment on etomidate-induced myoclonus. We investigated the influence of pretreatment with esketamine on the incidence of etomidate-induced myoclonus.

Methods: This is a prospective, double-blind, and randomized controlled trial. One hundred patients aged 18–65 scheduled for elective surgery under general anesthesia (including urology surgery, gynaecology surgery, general surgery, and thoracic surgery) were randomly allocated into two groups, each consisting of 50 patients. Esketamine was pretreated with 0.1 mg/kg 60 s before the initiation of etomidate in Group ESK, while normal saline was administered as the placebo (Group C). During the first 1 minute after etomidate administration, myoclonus incidence and severity were assessed. In addition, we measured the hemodynamic changes and side effects of esketamine before administering etomidate.

Results: In group ESK, 14 patients (28%) had myoclonus (degrees of myoclonus: mild 2, moderate 7, severe 5), and 32 patients (64%) in group C (mild 6, moderate 5, severe 21) ($P< 0.001$). In group ESK, myoclonus incidence and severity were significantly lower than in group C ($P< 0.001$).

Conclusion: Esketamine 0.1mg/kg IV pretreatment significantly reduce the incidence and the severity of severe myoclonus of etomidate-induced myoclonus without significant adverse effects.

Keywords: esketamine, etomidate, myoclonus, anesthesia induction

Introduction

Etomidate is commonly employed as an induction agent for its beneficial characteristics, including its hemodynamic stability, minimal respiratory depression, and pharmacokinetic properties that allow rapid recovery.[1] Myoclonus, however, is the most common side effect of etomidate.[2,3] In patients who are not pretreated for etomidate-induced myoclonus, the rate ranges from 50% to 80%,[2,4] which may lead to patient discomfort. Aspiration and regurgitation may occur more frequently under emergency situations when myoclonic movements occur. Etomidate-induced myoclonus may also serve as a problem in the patients who have limited cardiovascular reserves and patients with open globe injuries, which refers to full-thickness injuries to the eye wall.[5] Myoclonic movements should be avoided after etomidate administration. A variety of agents, including opioids, propofol, dexmedetomidine, midazolam, lidocaine, ketamine and magnesium sulfate, reduced the incidence of myoclonus.[6–10] Pretreatment with N-methyl-d-aspartate (NMDA) receptor antagonists such as ketamine and magnesium sulfate to prevent etomidate-induced myoclonus has been reported. Esketamine, a NMDA receptor antagonist, was widely used anesthetic and treated depression in clinical practice.[11]

Received: 28 August 2024
Accepted: 25 November 2024
Published: 5 December 2024

However, there has been no study about the effects on myoclonus after etomidate injection inpatients pretreated with esketamine.

Therefore, the purpose of this study was to investigate the effect of pretreatment with esketamine on the incidence and severity of etomidate-induced myoclonus during induction of anesthesia with etomidate.

Methods

Study Design

This was a prospective randomized double blinded study. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. This research was authorized by the Review Board of the First Affiliated Hospital of Anhui Medical University and the ethics committee of Anhui Medical University (PJ-2023-07-19). Before enrolling patients, the trial was registered on chictr.org.cn (ChiCTR2300074192, Principal Investigator: Lijian Chen, Date of Registration: 2023-8-1) and all participants provided signed informed consent.

Study Participants

The study was conducted from August 2023 to November 2023 at the First Affiliated Hospital of Anhui Medical University, where a total of 108 patients were screened. Of these, 100 participants scheduled for elective surgery were recruited, meeting the inclusion criteria of being aged between 18 and 65, having an ASA classification of I–III, and identifying as any sex. In addition, participants who met the following criteria were excluded: Pregnant patients, patients with adrenal cortical dysfunction, patients with neurological disorders or mental disorders, study patients with drug allergies, patients who have taken pain killers, sedatives, or opioid drugs within the past 24 hours, obesity (BMI>30kg/m2), patients with difficult airways, severe liver or kidney dysfunction, patients with severe cardiovascular diseases, stomach full patients.

Study Procedure

All the included participants were randomly allocated into the esketamine group (Group ESK) or the placebo group (Group C) at a ratio of 1:1 using computer-generated block randomization (block size, 4) by an investigator, each consisting of 50 patients. We kept the results of the randomization in sealed opaque envelopes before preparing the study drugs. Group ESK was pretreated with 0.1 mg/kg esketamine for 60 s before induction with etomidate (0.3mg/kg), and Group placebo received the same volume of normal saline as the control group. During the recording of myoclonus intensity, both patients and anesthesiologists were blinded to the group they were assigned to. Pretreatment drugs were prepared in a 20-mL syringe by the anesthesiologist who was not involved in the anesthesia induction.

Upon arrival in the operating room, patients underwent routine monitoring, which included noninvasive blood pressure, electrocardiogram, and oxygen saturation. Venous access was confirmed, and patients were oxygenated before receiving the study drug prior to anesthesia induction. No additional drugs were administered before the study drug. Anesthesia was induced with etomidate over a 20-second period, and patients were monitored for myoclonus episodes 1 minute after the injection of etomidate. Another anesthesiologist recorded myoclonic movements on a scale between 0–3. The intensity of myoclonus was graded clinically as 0 no myoclonus, 1 mild myoclonus (movement at the wrist only), 2 moderate (movement involving the arm only, elbow, or shoulder), and 3 severe (generalized response or movement in more than one extremity), following the etomidate injection.[2] The mean arterial pressure (MAP) and heart rate (HR) were recorded before the esketamine injection (T0), 1 minute after the esketamine injection (T1), 1 minute after the etomidate injection (T2), and 1 minute after the induction drug injection (T3). As soon as the observation period ended, 0.03 mg/kg midazolam, 0.4 g/kg sufentanil, and 0.2 mg/kg Cisatracurium was administered for the induction of anesthesia. Following intubation with an appropriately sized endotracheal tube, standardized anesthesia and analgesia protocols were administered.

Study Outcomes

The primary outcome of our study was the incidence of etomidate-induced myoclonus. The secondary outcomes were the severity of myoclonus, and esketamine-related adverse effects (nausea and vomiting, hallucinations, hypertension, tachycardia, and respiratory depression).

Statistical Analysis

The sample size was determined utilizing the Power and Sample Size Program 3.0.43. Based on prior research indicating a 72% incidence of myoclonus following etomidate administration,[4] and assuming a 30% reduction in myoclonus frequency post-administration, a minimum sample size of 48 patients per group was determined based on a power of 85% and a two-tailed α-error of 5%. Ultimately, it was determined that 50 patients would be allocated to each group.

Data are expressed as the mean ± standard deviation or percentages. In this study, T-tests were used to compare the demographic data of the patients and their vital signs between the two groups. In order to analyze etomidate-induced myoclonus frequency, ASA class, and gender, we used the chi-squared test. We used the Mann–Whitney *U*-test to test the effect of low-dose esketamine on the severity of myoclonic movements. SPSS 13.0 was employed for the statistical analysis of the data, with a significance level of $P < 0.05$ being deemed as statistically significant.

Results

In the current study, 100 out of 108 consecutive patients met the inclusion criteria and provided informed consent to participate. These 100 patients were subsequently randomized into two groups of 50 each (Figure 1). Notably, there were no dropouts or losses to follow-up. Demographic characteristics were not significantly different between the two groups (Table 1). The frequency of myoclonus was significantly higher in patients in the placebo group (32/50, 64%) compared to those in the esketamine pretreatment group (14/50, 28%; $P<0.001$). Therefore, pretreatment with esketamine significantly reduced etomidate-induced myoclonus after the administration of esketamine. The severity of myoclonus

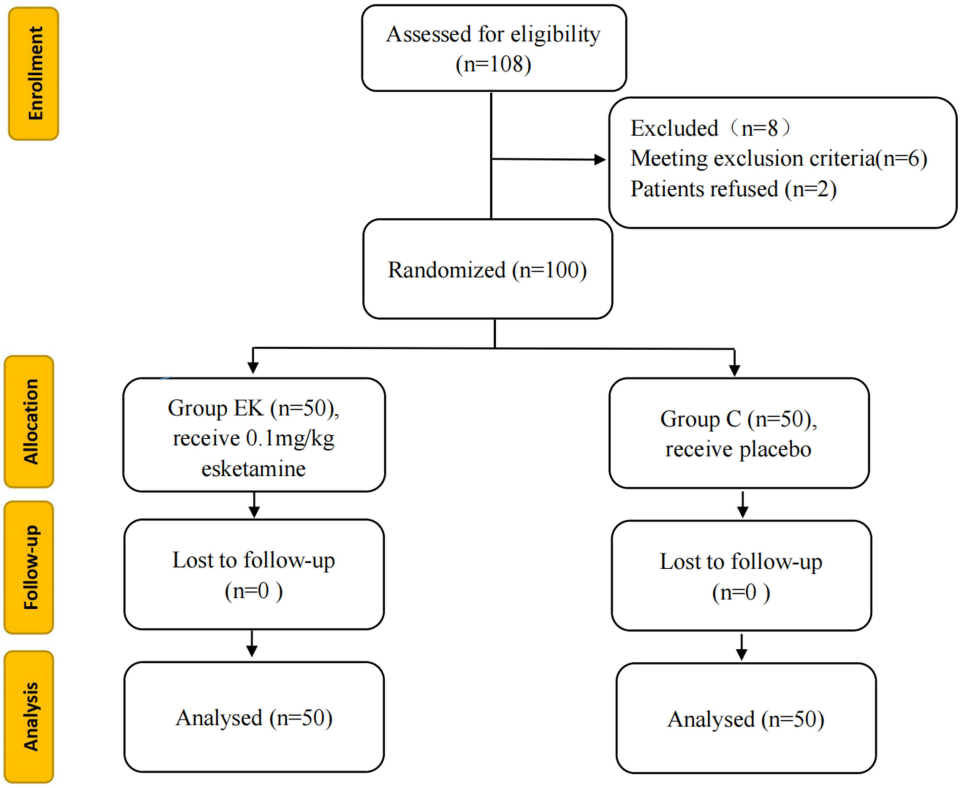

Figure 1 The clinical procedures for the study followed the CONSORT flow. Group ESK was given 0.1 mg/kg esketamine 60 seconds before etomidate induction, while Group C received a placebo of normal saline in the same volume.

Table 1 Demographic Data of the Patients Receiving Esketamine or Placebo

	Group ESK (n=50)	Group C (n=50)	P-value
Age	45.4±11.2	44.2±11.4	0.563
Sex			0.542
Male	22	19	
Female	28	31	
BMI	23.7±2.8	24.3±3.4	0.072
Hypertension			0.617
Yes	9	11	
No	41	39	
Diabetes			1
Yes	3	3	
No	47	47	
ASA physical status			1
1	4	5	
2	45	45	
3	1	0	
Type of surgery			0.817
Urology surgery	29	27	
Gynaecology surgery	9	13	
General surgery	8	7	
Thoracic surgery	4	3	

Notes: Values are expressed as mean±standard deviation, gender, ASA physical status, comorbidities, and type of surgery as number. Group ESK=0.1 mg/kg esketamine, Group C= placebo. No statistical difference was observed in this table.

was also significantly lower in group ESK than in the placebo (Table 2). At each time point, the MAP (mean arterial blood pressure) and HR (the heart rate) were not significantly different between the two groups (Figure 2). In terms of any other side-effect, no statistically significant differences were observed among the groups (Table 3). Esketamine showed respiratory depression in only one patient, whereas placebo showed no respiratory depression. However, it can be relieved by jaw thrust.

Discussion

We observed that pretreatment with esketamine 0.1 mg/kg reduced the incidence of myoclonus after induction with etomidate without significant adverse effects. The incidence of myoclonus was 28% in the esketamine group and 64% in the placebo group.

Table 2 Incidence of Etomidate–Induced Myoclonus

Myoclonus	Group ESK (n=50)	Group C (n=50)	P-value
Incidence [No. (%)]	14 (28%) *	32 (64%)	<0.001
The severity of myoclonus [No. (%)]			<0.001
None	36 (72%) *	18 (36%)	
Mild	2 (4%)	6 (12%)	
Moderate	7 (14%)	5 (10%)	
Severe	5 (10%)	21 (42%)	

Notes: Data are given as number of patients (%). Group ESK=0.1 mg/kg esketamine, Group C= placebo. * $P < 0.001$ vs group C.

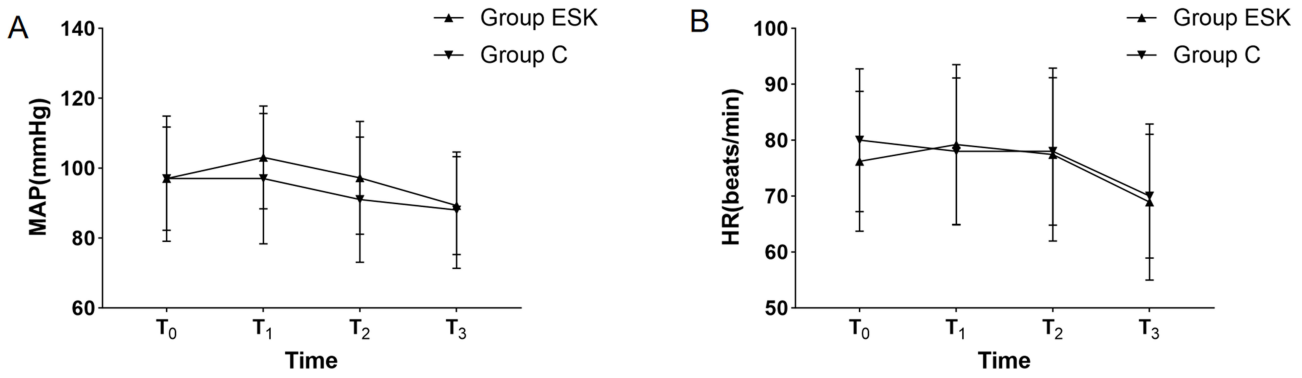

Figure 2 Vital signs change after treatment. (**A**) MAP (mmHg); (**B**) HR (beats/min); Group ESK = 0.1 mg/kg esketamine; Group C = placebo. MAP and HR were not significantly different at each time point between the two groups.

Abbreviations: MAP, mean arterial pressure; HR, heart rate; T0, time before administration of esketamine or normal saline injection; T1, 1 minute after administration of esketamine or normal saline injection; T2, 1 minute after the etomidate injection; T3, 1 minute after the induction drug injection.

Low dose esketamine may have some other benefits. In previous study, Xie et al found that analgesia pumps with low-dose esketamine infusion effectively relieve postoperative pain in pediatric urology patients.[12] Wang et al showed that a low-dose of esketamine can reduce postpartum depression following cesarean delivery.[13] Although injection pain caused by etomidate has been solved by using a lipid formulation, pretreatment with a low-dose esketamine can reduce the incidence of propofol injection pain.[14] Additionally, the research revealed that the incidence of cough induced by sufentanil was significantly diminished with premedication of 0.15 mg/kg esketamine.[15]

The pretreatment with opioids prior to induction of anesthesia with etomidate has been shown to reduce myoclonus.[16] Pretreatment with 100 ug of fentanyl reduced the incidence of myoclonus to 8%.[17] However, in other study, Bisht M et al found that the incidence of myoclonus 32.5% on pretreatment with 2 μg/kg dose of fentanyl.[18] Also, fentanyl-induced cough immediately before induction of anesthesia occurs in about 30% of non-pretreated patients.[19] The incidence of myoclonus was reduced to 8% following pretreatment with 0.2 mg/kg nalbuphine.[16] Nevertheless, the administration of nalbuphine via intravenous injection may result in significant pain localized at the site of injection. Research has shown that sufentanil 0.3μg/kg is efficacious in mitigating myoclonus. But patients administered this drug exhibited increased sedation levels and decreased respiratory rates.[6] The efficacy of alternative opioids, such as alfentanil and buprenorphine, have not been shown to prevent etomidate-induced myoclonus by studies.[16] Elevated doses of opioids have been shown to effectively reduce myoclonic movements, however, this therapeutic benefit is accompanied by a range of undesirable adverse effects such as coughing, sedation, respiratory depression, apnea, and chest wall rigidity.[6]

It has also been investigated whether pretreatment with benzodiazepine reduces myoclonus associated with etomidate. Schwarzkopf et al reported that 0.015 mg/kg midazolam pretreatment significantly reduced the incidence of myoclonic movements compared with placebo.[1] However, patients may experience a prolonged recovery period from benzodiazepines. Propofol decreased etomidate-induced myoclonus in adult patients, according to a meta-analysis and systematic review. Nevertheless, pretreatment with propofol may not be suitable for patients with limited cardiovascular reserves. Pretreatment with dexmedetomidine 0.5 μg/kg allows for a 38% reduction in the incidence of etomidate-induced

Table 3 Number of Adverse-Effects

Side effects	Group ESK (n=50)	Group C (n=50)
Hypertension	1	0
Tachycardia	3	2
Respiratory depression	1	0
Hallucination	0	0
Nausea/vomiting	0	0

Notes: Data are given as number of patients (%). Group ESK=0.1 mg/kg esketamine, Group C= placebo. * $P < 0.001$ vs group C.

myoclonus.[20] Dexmedetomidine exhibits a long onset time necessitating administration 15 minutes prior to induction, thereby constraining its use in clinical practice.

Etomidate-induced myoclonus has also been reduced by NMDA receptor antagonism pretreatment. Guler et al[4] found that administering 2.48 mmol of magnesium 90 seconds prior to the induction of anesthesia with etomidate has been shown to effectively mitigate the severity of etomidate-induced myoclonus. The incidence of myoclonus following magnesium pretreatment is comparable to that observed with pretreatment with esketamine. A low-dose ketamine infusion given 60s before etomidate administration effectively mitigates etomidate-induced myoclonic movements during general anesthesia induction by Wu, Guan Nan et al.[21] Other studies indicate that ketamine was not effective in reducing the myoclonus and it caused respiratory depression and sedation.

Lidocaine pretreatment also reduced the incidence of myoclonic movements compared with placebo. A meta-analysis indicated that pretreatment with lidocaine can reduce the incidence of etomidate-induced myoclonus,[22] but the incidence of etomidate-induced myoclonus in the experimental group remained elevated at 37.6%. Additional drugs, such as muscle relaxants, have the potential to decrease the incidence of myoclonus. Pretreatment with 0.06 mg/kg rocuronium before induction of anesthesia with etomidate significantly reduced the frequency of myoclonus.[23] However, the primary disadvantage of pretreatment with rocuronium is the discomfort experienced upon injection pain.

Although a number of drugs have been tested to decrease the incidence of myoclonus, the neurologic mechanism of myoclonus induced by etomidate is unclear.[2,24] Several mechanisms have been proposed to interpret etomidate-induced myoclonus. Suttmann et al[25] posited that the myoclonic movement triggered by etomidate is a manifestation of disinhibition, as higher doses of etomidate are observed to suppress cortical activity prior to subcortical activity. As demonstrated by Doenicke et al[2], myoclonus after injection of etomidate is caused by subcortical disinhibition, similar to restless legs while sleeping. However, many studies suggested that the etomidate-induced myoclonus may be associated with seizure.[26]

In our study, esketamine reduced the incidence of etomidate-induced myoclonus. In status epilepticus, esketamine may be effective at treating seizures by blocking glutamatergic neurotransmission mediated by (NMDA) the N-methyl-D-aspartate receptor.[27] Furthermore, other study[28] reported that the administration of low-dose ketamine successfully alleviated myoclonus in a patient undergoing prolonged opioid therapy.

The available literature did not include any research about esketamine and myoclonus. The analgesic and anesthetic effects of esketamine are approximately two to three times that of ketamine. Therefore, I chose a concentration of 0.2mg/kg of esketamine for preventing etomidate-induced myoclonus based on the ketamine dose in prior studies during pre-test. However, this dosage frequently results in significant hypertension during the induction phase. I conducted a review of the existing literature in order to find the minimal dosage of esketamine in clinical practice.[29] As a result, we chose the dose of 0.1mg/kg esketamine. Finally, the results of our study indicate that pretreatment with 0.1mg/kg esketamine resulted in a significant reduction in myoclonus induced by etomidate. Although, there are various concerns regarding the use of esketamine, such as heightened intracranial pressure, elevated intraocular pressure, psychodysleptic effects, and paradoxical myocardial depression. Neither the above adverse effects nor related symptoms were noted, which is consistent with early studies showing low-dose esketamine is safe and has a low rate of adverse reactions.[30,31]

Our study had some limitations. Firstly, we did not examine the effects of other doses of esketamine on etomidate-induced myoclonus incidence, higher doses of esketamine may cause its potential adverse effects. Next, we will determine the optimal clinically effective dosage of esketamine for mitigating etomidate-induced myoclonus. Furthermore, this research was only carried out at a singular research facility. A further study will evaluate the effects of esketamine on the frequency of myoclonus induced by etomidate with different hospitals. Finally, we did not compare the effects of esketamine and ketamine on etomidate-induced myoclonus incidence. This research indicates that pretreatment with esketamine resulted in a significant reduction in myoclonus induced by etomidate. A further research will compare the effects of esketamine and ketamine on the frequency of myoclonus induced by etomidate.

Conclusion

In summary, the results of this study indicate that pretreatment with 0.1mg/kg esketamine resulted in a significant reduction in myoclonus induced by etomidate. Therefore, the use of esketamine as a pretreatment offers a viable strategy for mitigating etomidate-induced myoclonus during anesthesia induction.

Data Sharing Statement

The datasets used during the current study are available from corresponding authors on reasonable request.

Acknowledgment

The study was registered in the Chinese Clinical Trial Registry (ChiCTR2300074192, Principal investigator: Lijian Chen, Date of registration: 2023-8-1).

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

Conflicts of interest are not declared by any of the authors.

References

1. Schwarzkopf KR, Hueter L, Simon M, Fritz HG. Midazolam pretreatment reduces etomidate-induced myoclonic movements. *Anaesth Intensive Care*. 2003;31(1):18–20. doi:10.1177/0310057X0303100103
2. Doenicke AW, Roizen MF, Kugler J, Kroll H, Foss J, Ostwald P. Reducing myoclonus after etomidate. *Anesthesiology*. 1999;90(1):113–119. doi:10.1097/00000542-199901000-00017
3. Lim TA, Lim KY. BIS during etomidate-induced myoclonus. *Anaesthesia*. 2006;61(4):410–411. doi:10.1111/j.1365-2044.2006.04601.x
4. Guler A, Satilmis T, Akinci S, Celebioglu B, Kanbak MJA. Magnesium sulfate pretreatment reduces myoclonus after etomidate. *Anesthesia Analg*. 2005;101(3):705–709. doi:10.1213/01.ANE.0000160529.95019.E6
5. Berry J, Merin RJ. Etomidate myoclonus and the open globe. *Anesthesia Analg*. 1989;69(2):256–259. doi:10.1213/00000539-198908000-00022
6. Hueter L, Schwarzkopf K, Simon M, Bredle D, Fritz HJ. Pretreatment with sufentanil reduces myoclonus after etomidate. *Acta anaesthesiologica Scandinavica*. 2003;47(4):482–484. doi:10.1034/j.1399-6576.2003.00081.x
7. Kelsaka E, Karakaya D, Sarihasan B, Baris SJ. Remifentanil pretreatment reduces myoclonus after etomidate. *J Clin Anesthesia*. 2006;18(2):83–86. doi:10.1016/j.jclinane.2005.05.004
8. Rajesh SR, Michell G, Pramod K, Rashmi S, Medha M, Kshitiz V. Comparative assessment of dexmedetomidine and butorphanol for attenuation of etomidate-induced myoclonus: a double-blind, randomised controlled study. *J Indian J Anaesth*. 2023;67(9):815–820.
9. Feng Y, Chen XB, Zhang YL, Chang P, Zhang WS. Propofol decreased the etomidate-induced myoclonus in adult patients: a meta-analysis and systematic review. *Eur Rev Med Pharmacol Sci*. 2023;27(4):1322–1335. doi:10.26355/eurrev_202302_31366
10. Gultop F, Akkaya T, Bedirli N, Gumus H. Lidocaine pretreatment reduces the frequency and severity of myoclonus induced by etomidate. *J Anesthesia*. 2010;24(2):300–302. doi:10.1007/s00540-010-0869-6
11. Jennifer S, Rejish KT, Shaina A, et al. Esketamine for treatment resistant depression. *J Expert Rev Neurother*. 2019;19(10):899–911.
12. Xie Y, Liang Z, Chen S, et al. Effectiveness of perioperative low-dose esketamine infusion for postoperative pain management in pediatric urological surgery: a prospective clinical trial. *BMC Anesthesiol*. 2024;24(1):65. doi:10.1186/s12871-024-02450-8
13. Wang Y, Zhang Q, Dai X, Xiao G, Luo H. Effect of low-dose esketamine on pain control and postpartum depression after cesarean section: a retrospective cohort study. *Ann Palliative Med*. 2022;11(1):45–57. doi:10.21037/apm-21-3343
14. Fu D, Wang D, Li W, Han Y, Jia J. Pretreatment with low-dose esketamine for reduction of propofol injection pain: a randomized controlled trial. *Pain Res Manag*. 2022;2022:4289905. doi:10.1155/2022/4289905
15. Liangliang G, Zhuoliang Z, Yi Z, Xinyu L, Yue T, Lei W. Effect of pretreatment with a small dose of esketamine on sufentanil-induced cough during anesthesia induction: a randomized controlled trial. *BMC Anesthesiol*. 2024;24(1).
16. Gupta M, Gupta P. Nalbuphine pretreatment for prevention of etomidate induced myoclonus: a prospective, randomized and double-blind study. *J Anaesthesiol Clin Pharmacol*. 2018;34(2):200–204. doi:10.4103/joacp.JOACP_210_16
17. He L, Ding Y, Chen H, Qian Y, Li Z. Butorphanol pre-treatment prevents myoclonus induced by etomidate: a randomised, double-blind, controlled clinical trial. *Swiss Med Weekly*. 2014;144:w14042. doi:10.4414/smw.2014.14042
18. Megha B, Abhimanyu Singh P, Gurjeet K, Jagdish PS. Effect of fentanyl and nalbuphine for prevention of etomidate-induced myoclonus. *Anesth Essays Res*. 2019;13(1):119–125.
19. Peringathara B, Robinson S. Fentanyl-induced cough is a risk factor for postoperative nausea and vomiting. *Br J Anaesth*. 2016;117(2):269. doi:10.1093/bja/aew207
20. Shuai M, Lan Z, Guanglei W, Xiuli W, Su L, Mengzhu S. Effect of dexmedetomidine on etomidate-induced myoclonus: a randomized, double-blind controlled trial. *Drug Des Devel Ther*. 2019;13.
21. Wu G, Xu H, Liu F, Wu X, Zhou H. Low-dose ketamine pretreatment reduces the incidence and severity of myoclonus induced by etomidate: a randomized, double-blinded, controlled clinical trial. *Medicine*. 2016;95(6):e2701. doi:10.1097/MD.0000000000002701
22. Bingchen L, Lingli Z, Chunsong Y, Yunzhu L, Wensheng Z, Fengshan L. Pretreatment with lidocaine reduces both incidence and severity of etomidate-induced myoclonus: a meta-analysis of randomized controlled trials. *Drug Des Devel Ther*. 2018;12:3311–3319.

23. Choi J, Choi I, Jeong Y, Kim T, Hahm K. Pretreatment of rocuronium reduces the frequency and severity of etomidate-induced myoclonus. *J Clin Anesthesia*. 2008;20(8):601–604. doi:10.1016/j.jclinane.2008.06.010
24. Wang J, Li QB, Wu YY, Wang BN, Kang JL, Xu XW. Efficacy and safety of opioids for the prevention of etomidate-induced myoclonus: a meta-analysis. *Am J Therapeutics*. 2018;25(5):e517–e523. doi:10.1097/MJT.0000000000000404
25. Suttmann H, Doenicke A, Kugler J, Laub M. A new formulation of etomidate in lipid emulsion--bioavailability and venous provocation. *Anaesthesist*. 1989;38(8):421–423.
26. Feng Y, Chang P, Kang Y, et al. Etomidate-induced myoclonus in Sprague-Dawley rats involves neocortical glutamate accumulation and N -methyl-D -aspartate receptor activity. *Anesthesia Analg*. 2023;137(1):221–233. doi:10.1213/ANE.0000000000006292
27. Alkhachroum A, Der-Nigoghossian CA, Mathews E, et al. Ketamine to treat super-refractory status epilepticus. *Neurology*. 2020;95(16):e2286–e2294. doi:10.1212/WNL.0000000000010611
28. Kolesnikov Y, Jain S, Wilson R, Pasternak G. Blockade of morphine-induced hindlimb myoclonic seizures in mice by ketamine. *Pharmacol Biochem Behav*. 1997;56(3):423–425. doi:10.1016/S0091-3057(96)00221-3
29. Yongtong Z, Shuqing L, Zecheng Y, et al. Efficacy and safety of subanesthetic doses of esketamine combined with propofol in painless gastrointestinal endoscopy: a prospective, double-blind, randomized controlled trial. *BMC Gastroenterol*. 2022;22(1):391.
30. Luo J, Yin K, Zhao D, Zhang Z, Sun R. Effect of intravenous induction with different doses of Esketamine combined with propofol and sufentanil on intraocular pressure among pediatric strabismus surgery: a randomized clinical trial. *BMC Anesthesiol*. 2023;23(1):275. doi:10.1186/s12871-023-02238-2
31. Eberl S, Koers L, van Hooft J, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: a randomised controlled multicentre trial. *European J Anaesthesiol*. 2020;37(5):394–401. doi:10.1097/EJA.0000000000001134