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Effect of Pretreatment with a Small Dose of Esketamine on Myoclonus Induced by Etomidate: A Randomized Controlled Trial

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Background: Etomidate has been observed to precipitate myoclonus in patients undergoing induction of general anaesthesia. This study was designed to investigate the effect of pretreatment with a small dose of esketamine on the incidence of myoclonus induced by etomidate.

Methods: One hundred adult patients, who were scheduled to undergo selective operations with general anesthesia, were randomly divided into two groups, with one group receiving esketamine (Group E) and the other receiving normal saline (Group C). The group receiving esketamine (Group E) was administered an injection of 0.15 mg/kg of esketamine, while the control group (Group C) was given an equivalent volume of normal saline two minutes before the administration of 0.3 mg/kg of etomidate. The primary objective was to determine the incidence of etomidate-induced myoclonus. Secondary endpoints included the severity of etomidate-induced myoclonus and changes in haemodynamic variables at various time intervals. Additionally, the incidence of adverse effects such as dizziness, bradycardia, hypotension and hallucination were recorded from the administration of esketamine or normal saline to the injection of etomidate.

Results: The incidence of myoclonus was significantly lower in Group E (20%) than in Group C (62%). Compared with the control group, the esketamine group also experienced a reduction in the moderate and severe of myoclonus. However, there was no statistically significant difference between the two groups for mild etomidate-induced myoclonus. The haemodynamic data (mean arterial pressure and heart rate) showed no statistically significant differences between two groups at the three time points. The incidence of dizziness, bradycardia, hypotension and hallucination was similar in both groups.

Conclusion: Pretreatment with 0.15 mg/kg esketamine prior to anaesthesia induction with etomidate was observed to markedly reduce the incidence and severity of myoclonus, while having no effect on mild etomidate-induced myoclonus and maintaining a stable haemodynamic status.

Keywords: esketamine, etomidate, myoclonus, pretreatment

Introduction

Etomidate is recommended as a anaesthetic agent for patients with compromised cardiovascular function, due to its minimal cardiopulmonary side effects and stable cardiovascular profile.[1] However, the administration of etomidate may be associated with certain unfavourable effects such as pain on injection and myoclonus. Pain on injection has been alleviated by the implementation of a lipid formulation of etomidate.[2] However, etomidate-induced myoclonus remains a significant clinical concern, with an incidence rate of 50% to 80% in patients who have not received premedication.[3,4] Myoclonic movements have the potential to cause patient discomfort, present a challenge for those with partial cardiovascular reserves, and increase the risk of aspiration for those with a full stomach. Moreover, myoclonus may result in elevated intraocular pressure, which can present complications in patients undergoing open-eye surgery.[5,6]

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Although the underlying mechanisms of myoclonus are not fully comprehended, various interventions have been adopted to prevent the emergence of myoclonus during the induction phase of anesthesia, including lidocaine,[6] midazolam,[7] opioids,[8,9] dexmedetomidine,[10] or ketamine[11] as well as with non-pharmacological approaches like transcutaneous acupoint electrical stimulation[12] and extend injection time.[1] The implementation of these interventions extensively in clinical practice is currently not feasible due to the various adverse effects they can cause, which include onset time, hypotension, heart rhythm, cough, respiratory depression and chest wall rigidity. Esketamine, an inhibitor of the N-methyl-D-aspartate (NMDA) receptor, has been demonstrated to confer beneficial effects during surgical procedures, including sedation, anti-anxiety properties and analgesia. Furthermore, it has been observed to have a lower incidence of adverse events in comparison to ketamine.[13,14] To the best of our knowledge, no study has yet evaluated the effect of esketamine etomidate-induced myoclonus. The aim of the present study was to examine the impact of esketamine pretreatment on the incidence and severity of myoclonus induced by etomidate.

Methods

This prospective, randomised controlled study was conducted between October 2023 and April 2024 in the First Affiliated Hospital of Anhui Medical University. Prior to the commencement of the study, approval was obtained from the hospital ethics committee, and written informed consent was obtained from all subjects participating in the trial. Prior to the commencement of patient enrolment, the trial was registered at www.chictr.org.cn (ChiCTR2300074192). This study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.

Patients

The study population comprised 100 patients of either sex, aged between 18 and 65 years, with a physical status classification of I or II according to the American Society of Anesthesiologists (ASA), and undergoing elective surgical procedures under general anaesthesia. Exclusion criteria included BMI > 30kg/m^2, patients with adrenal cortical dysfunction, neurological disorders or mental disorders, drug allergies, severe liver or kidney dysfunction, severe cardiovascular diseases. Additionally, patients who had taken painkillers, sedatives, or opioid drugs within the past 24 hours were also excluded.

Randomisation and Blinding

Patients were randomly assigned in a 1:1 ratio to receive either esketamine or an equivalent volume of saline using a computer-generated randomisation table. To ensure the concealment of group assignments, these were placed in sealed envelopes, which were then handed sequentially to a nurse who was not involved in the study. The esketamine and saline solutions were prepared in identical 20-mL syringes by the same nurse. The patients and anaesthesiologists involved in the management of the patients were blinded to the group assignment. To eliminate the bias of the outcome assessor who observed myoclonus, one anesthesiologist who was blind to the group allocation and did not participate in the study further recorded hemodynamic variables and side effects. Blinded to the group assignment, the other anesthesiologist evaluated the frequency and intensity of myoclonus.

Study Protocol

A routine intraoperative monitoring protocol was implemented, encompassing pulse oximetry, electrocardiography, and non-invasive blood pressure measurement. A 20G intravenous cannula was secured into a vein on the dorsum of the hand and attached to a Ringer lactate drip. Prior to the administration of anaesthesia, the patients were administered oxygen 6 L/min. Prior to etomidate induction, group E was pretreated with 0.15 mg/kg esketamine, while group C was pretreated with an equivalent volume of normal saline. Two minutes following the administration of the study drug, 0.3 mg/kg etomidate was administered over 30 seconds. The grading of myoclonus is as follows: The severity of myoclonus was classified as follows: 0 (none), 1 (mild: movement at the finger or wrist only), 2 (moderate: slight movements in one part of the body, such as the face or legs), or 3 (severe: generalized response or fast abduction of a limb).[15] The patients were observed for the occurrence of myoclonus over the subsequent two minutes. Following the two-minute observation period, 0.3 μg/kg sufentanil and 0.2 mg/kg cisatracurium were administered to both groups to facilitate tracheal

intubation. Anesthesia was maintained with propofol 4–6 mg/(kg·h) and remifentanil 0.1–0.3 μg/(kg·min) until 10 minutes prior to the completion of surgery. Mechanical ventilation was administered to maintain an end-expiratory carbon dioxide concentration of 35–40 mmHg. The residual neuromuscular blockade was antagonised with neostigmine and atropine following the completion of surgery. In the event of a decrease in mean arterial pressure (MAP) below 60 mmHg (or below 80% of the baseline value), 6 mg of ephedrine was administered to restore blood pressure. Bradycardia (heart rate below 45 beats per minute) was addressed with atropine 0.5 mg.

Outcome Measurements

The primary outcome was the incidence of myoclonus during the two minutes following the administration of etomidate. The secondary outcomes included the severity of myoclonus induced by etomidate, the incidence of adverse effects resulting from pretreatment with esketamine or normal saline prior to the administration of etomidate, such as dizziness, bradycardia, hypotension, and hallucinations. Moreover, mean arterial pressure and heart rate were evaluated at the following time points: T_0 (baseline), T_1 (five minutes following the induction of anesthesia), and T_2 (five minutes after the initiation of the operation).

Sample Size Calculation

The PASS 11 program (PASS, Kaysville, UT, USA) was employed to estimate the required sample size. According to previous study,[16] It was anticipated that the incidence of myoclonus in the control group would be 0.7. A power analysis indicated that a 40% reduction in the incidence of myoclonus with an alpha level of 0.05 and a 10% dropout rate within an 80% power could be detected with a sample size of at least 50 per group.

Statistical Analysis

The statistical analysis was conducted using the IBM SPSS Statistics software, version 21.0. The normality of the variables was assessed using the Shapiro–Wilk test. Continuous data were presented as mean ± standard deviation and compared using the unpaired, 2-tailed *t*-test. Categorical variables were reported as numbers and compared using the chi-squared or Fisher exact test. The analysis of repeated measures variables was conducted using repeated measures analysis of variance. A two-sided *P* value of less than 0.05 was considered to be statistically significant.

Results

Out of the 126 consecutive patients who were assessed for eligibility, 100 met the criteria for inclusion and were therefore included in the study (eight patients declined to participate, and eighteen patients' anaesthetic plans were modified before the study began) (Figure 1). No significant differences were observed between the groups with regard to age, sex, height, weight, and ASA physical status (Table 1).

The administration of esketamine prior to the administration of etomidate resulted in a statistically significant reduction in the incidence of etomidate-induced myoclonus, with a 42% reduction observed (20% vs 62%, RR=0.32, 95% CI=0.215–0.523, *P*=0.003). A significantly lower moderate and severe of myoclonus was observed in group E within two minutes following etomidate injection, in comparison to group C ($P < 0.05$). However, there was no statistically significant difference in mild etomidate-induced myoclonus between the two groups ($P > 0.05$) (Table 2).

Mean arterial pressure and heart rate did not differ statistically significantly between the two groups during the three different times of general anaesthesia ($P > 0.05$) (Table 3 and Table 4).

The incidence of dizziness, bradycardia, hypotension and hallucination was comparable in the two groups ($P > 0.05$). One patient from Group E experienced dizziness, while two patients from the same group experienced hypotension. Three patients from Group C exhibited evidence of hypotension (Table 5).

Discussion

The present study demonstrated that pretreatment with 0.15 mg/kg esketamine prior to the induction of anaesthesia with etomidate could effectively reduce the incidence and severity of etomidate-induced myoclonus.

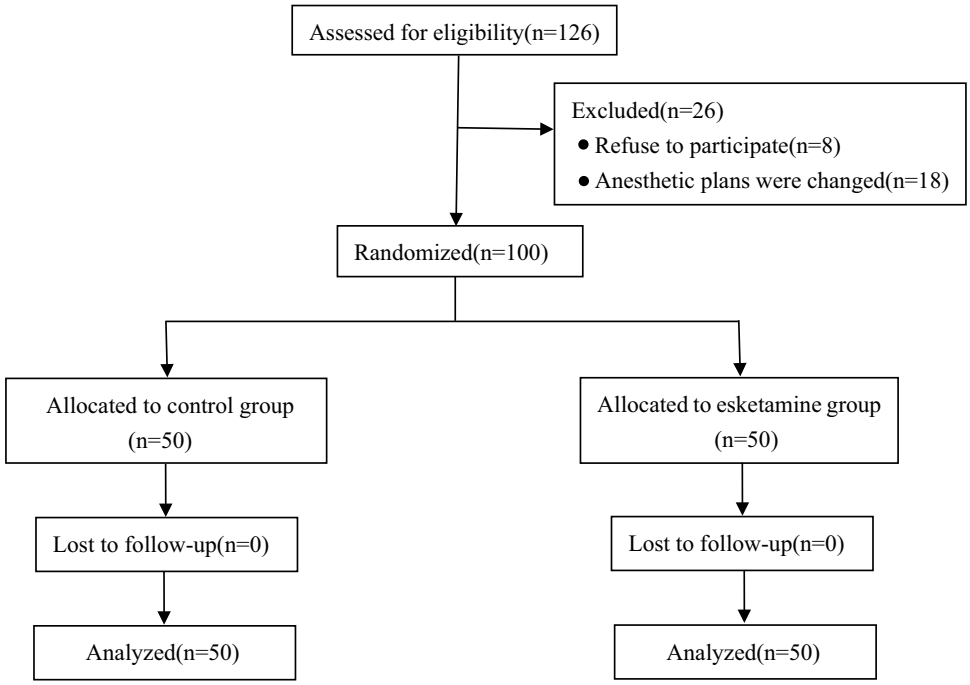

Figure 1 Study flow diagram.

Etomidate is an imidazole derivative that has been demonstrated to possess potent hypnotic properties and superior haemodynamic stability when compared to other induction agents.[17] Nevertheless, the most certain and undesirable side effect of etomidate is myoclonus. Etomidate-induced myoclonus was observed in 62% of subjects participating in this study. In a study conducted by Fethi et al[18] it was determined that the incidence of etomidate-induced myoclonus was 66% following the administration of etomidate at a dosage of 0.3 mg/kg within 20 seconds. In a study designed by Abbas et al, it was revealed that the administration of 0.3mg/kg etomidate within a period of 20 seconds could result in an incidence of myoclonus reaching 71.8%.[9] According to Parul et al, administering etomidate at a reduced injection rate

Table 1 Baseline Variables for Patients

	Control Group	Esketamine Group	*P*-value
Age (years)	45.8 ± 7.6	42.3 ± 8.5	0.431
Sex (Male: Female)	28:22	31:19	0.545
Height (cm)	167 ± 8.2	169 ± 9.1	0.726
Weight (kg)	68.3 ± 9.3	70.2 ± 8.7	0.683
ASA status (I: II)	21:29	24:26	0.344

Note: Data are expressed as mean ± SD, or number.
Abbreviation: ASA, American Society of Anesthesiologists.

Table 2 Incidence and Severity of Myoclonus After Etomidate Injection

	Control Group	Esketamine Group	*P*-value
None	19	40	0.003*
Mild	8	6	0.564
Moderate	11	3	0.021*
Severe	12	1	0.001*

Note: Data are expressed as number.

Table 3 Changes in MAP at Different Time Points of General Anesthesia

MAP (mmHg)	T_0	T_1	T_2
Control Group	97.68±10.20	88.48±12.35	93.18±10.67
Esketamine Group	95.81±11.24	90.95±11.87	92.70±12.53
P-value	0.764		

Table 4 Changes in HR at Different Time Points of General Anesthesia

HR (bpm)	T_0	T_1	T_2
Control Group	76.56±14.24	67.11±15.19	73.43±12.48
Esketamine Group	74.57±12.13	66.81±11.25	71.51±13.56
P-value	0.412		

Notes: Data are expressed as mean ± SD, T_0 (baseline), T_1 (5 minutes after anesthesia beginning), T_2 (5 minutes after operation beginning).
Abbreviations: MAP, mean arterial pressure; HR, heart rate.

Table 5 Adverse Effects in the Two Groups

Adverse Effects	Control Group	Esketamine Group	*P*-value
Dizziness	0	1	0.237
Bradycardia	0	0	>0.99
Hypotension	3	2	0.645
Hallucination	0	0	>0.99

Note: Data are expressed as number.

was found to be effective in minimizing the incidence of myoclonus.[1] In comparison to previous studies, the incidence of etomidate-induced myoclonus was found to be lower in this study. This may be attributed to the slower rate of intravenous etomidate administration.

It has been demonstrated that a number of pharmacological agents are effective in the prevention of etomidate-induced myoclonus, including lidocaine, midazolam, opioids, dexmedetomidine and ketamine. In a previous study, Fethi et al[19] indicted that the administration of intravenous lidocaine 20 mg for 30s prior to etomidate injection was an effective method to suppress etomidate-induced myoclonus. According to the findings of Lars et al[7] the use of midazolam at a concentration of 0.015 mg/kg, given 90 seconds before the induction of anesthesia with etomidate, is effective in lowering the rate of myoclonus. The investigation led by Lee SW and associates revealed that pretreating patients with remifentanil substantially lowered the rate and severity of myoclonus triggered by etomidate.[8] In a study led by Shuai Miao et al[10] it was discovered that administering dexmedetomidine at a dosage of 0.5 μg/kg prior to the induction of general anaesthesia could potentially reduce the incidence of myoclonus induced by etomidate. Hai Zhou et al showed that the intravenous administration of a low dose of ketamine (0.5 mg/kg) one minute prior to the administration of etomidate was an effective method of alleviating myoclonic movements induced by etomidate during general anaesthesia induction.[11] However, these drugs were accompanied by a number of potential side effects, including respiratory depression, hypotension and arrhythmias.

Esketamine and ketamine exhibit comparable pharmacological effects, acting as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. A previous study demonstrated that a low dose of ketamine was an effective method of reducing etomidate-induced myoclonus and delaying the onset of myoclonus.[11] Nevertheless, the utilisation of ketamine remains constrained by its hallucinogenic properties and the elevation of blood pressure, intracranial pressure, and intraocular pressure that occurs during general anaesthesia.[20] In comparison to ketamine, esketamine has been

demonstrated to exhibit a reduced incidence of adverse effects and a superior efficacy in the management of sedation and pain.[14,21] According to the result of previous study, 0.2mg/kg esketamine injection showed stable haemodynamics during anesthesia induction.[14] To eliminate the bias of the outcome, We chose esketamine at a dose of 0.15 mg/kg in this study. The incidence of moderate and severe myoclonus were significantly reduced in the esketamine group compared to that of the control group, as a result of the administration of etomidate in this study. Nevertheless, the occurrence of mild myoclonus was found to be comparable between the two groups.

Despite the testing of numerous pharmaceutical agents with the objective of reducing the prevalence of myoclonic activity following the administration of etomidate, the underlying neurological mechanism of etomidate-induced myoclonus remains uncertain. It is hypothesised that the involuntary myoclonic movements observed in patients administered etomidate are caused by subcortical disinhibition. A substantial dosage of etomidate has been observed to initially suppress cortical activity, subsequently leading to the inhibition of subcortical processes, which in turn results in the manifestation of myoclonus.[19,22] A number of studies have indicated that the myoclonus associated with etomidate administration may be linked to seizure-like activity.[5,23] Furthermore, a high concentration of etomidate has been observed to interact with the GABA receptors of the central nervous reticular activating system. The interruption of GABA neurons can result in the increased sensitivity of pathways associated with skeletal muscle control, thereby facilitating spontaneous nerve transmissions. Such occurrences may ultimately result in myoclonic muscle contractions.[8] The latest research findings indicate that etomidate-induced myoclonus has its origin in the neocortex.[24] In light of the findings of previous studies, it can be postulated that esketamine exerts an inhibitory effect on etomidate-induced myoclonus by modulating the activity of the NMDA receptor in the neocortex.

It is essential to take into account various limitations in the present research. The initial study did not assess the impact of esketamine dosage on the prevalence of etomidate-induced myoclonus. Further research is required to ascertain the impact of varying esketamine doses on the incidence and severity of etomidate-induced myoclonus during anaesthetic induction. Secondly, the study population does not represent the ideal population in which etomidate is used as the induction agent of choice. The validation of our results in patients with haemodynamic or cardiovascular instability represents a significant step forward. Thirdly, the primary outcome measure was subjective; however, no other accurate and convenient monitoring indicators were identified in previous clinical studies. Fourthly, this research is a single-center clinical trial. It can be concluded that further extensive multicentre randomised controlled trials are required in order to gain a fuller insight into the impact of esketamine on etomidate-induced myoclonus.

Conclusion

The findings of this study indicate that pretreatment with 0.15 mg/kg esketamine prior to the administration of etomidate resulted in a notable reduction in the frequency and severity of myoclonus. It can thereby be concluded that pretreatment with a small dose of esketamine represents an effective method of preventing etomidate-induced myoclonus during the induction of anaesthesia.

Data Sharing Statement

The authors are pleased to make the data pertaining to each identified participant available for review. The data set from this study, including all figures and tables, can be obtained by contacting the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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