Pharmaceutical Sciences and Drug Design
ISSN: 3062-4428
2023, Volume 3, Page No: 239-244

Available online at: www.galaxypub.co/page/journals

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Impact of Low-Dose Esketamine Pretreatment on Etomidate-Induced Myoclonus: A Randomized Controlled Trial

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Received: 27 September 2023; **Revised:** 05 December 2023; **Accepted:** 07 December 2023

ABSTRACT

Etomidate is known to trigger myoclonus during the induction of general anesthesia. This study aimed to evaluate whether pretreatment with a low dose of esketamine could reduce the occurrence of etomidate-induced myoclonus.One hundred adult patients scheduled for elective surgeries under general anesthesia were randomly assigned to two groups: the esketamine group (Group E) and the control group (Group C). Group E received 0.15 mg/kg of esketamine, while Group C received an equal volume of normal saline, administered two minutes before 0.3 mg/kg of etomidate. The primary outcome was the incidence of etomidate-induced myoclonus. Secondary outcomes included myoclonus severity, changes in haemodynamic parameters at different time points, and the occurrence of adverse effects such as dizziness, bradycardia, hypotension, and hallucinations from the time of pretreatment until etomidate injection.The incidence of myoclonus was significantly lower in Group E (20%) compared to Group C (62%). Pretreatment with esketamine also reduced moderate and severe myoclonus, though no significant difference was observed for mild myoclonus between the groups. Haemodynamic parameters, including mean arterial pressure and heart rate, did not differ significantly at any time point. The rates of dizziness, bradycardia, hypotension, and hallucination were comparable between groups.Administering 0.15 mg/kg of esketamine before etomidate induction significantly decreased the incidence and severity of myoclonus without affecting mild cases and maintained stable haemodynamic conditions.

Keywords: Pretreatment, Esketamine, Etomidate, Myoclonus

How to Cite This Article: Schmidt L, Weber J. Impact of Low-Dose Esketamine Pretreatment on Etomidate-Induced Myoclonus: A Randomized Controlled Trial. Pharm Sci Drug Des. 2023;3:239-44. https://doi.org/10.51847/guhTln09kf

Introduction

Etomidate is frequently recommended as an anesthetic for patients with impaired cardiovascular function due to its minimal cardiopulmonary side effects and stable haemodynamic profile [1]. Nonetheless, etomidate administration can lead to undesirable effects, including injection pain and myoclonus. Injection pain has been mitigated through the use of lipid formulations of etomidate [2], but etomidate-induced myoclonus remains a considerable clinical issue, with reported incidence rates ranging from 50% to 80% in patients who have not received premedication [3, 4]. Myoclonic movements can cause discomfort, pose risks for patients with limited cardiovascular reserves, increase the likelihood of aspiration in patients with a full stomach, and elevate intraocular pressure, which may complicate ophthalmic surgery [5, 6].

Although the mechanisms underlying etomidate-induced myoclonus are not fully understood, several pharmacological and non-pharmacological strategies have been employed to prevent its occurrence during anesthesia induction, such as lidocaine [6], midazolam [7], opioids [8, 9], dexmedetomidine [10], ketamine [11], transcutaneous acupoint electrical stimulation [12], and prolonging injection time [1]. However, broad clinical application of these interventions is limited due to potential adverse effects, including delayed onset, hypotension, arrhythmias, cough, respiratory depression, and chest wall rigidity. Esketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated benefits in surgical settings, providing sedation, anxiolysis, and

analgesia, while being associated with fewer adverse effects compared with ketamine [13, 14]. To date, no studies have investigated the impact of esketamine on etomidate-induced myoclonus. Therefore, the present study aimed to evaluate the effect of esketamine pretreatment on the incidence and severity of etomidate-induced myoclonus.

Materials and Methods

This prospective, randomized controlled trial was conducted from October 2023 to April 2024 at the First Affiliated Hospital of Anhui Medical University. Ethical approval was obtained from the hospital's ethics committee, and written informed consent was obtained from all participants. The trial was registered at www.chictr.org.cn (ChiCTR2300074192) and conducted in accordance with the Declaration of Helsinki.

Patients

The study included 100 patients aged 18–65 years, of either sex, with ASA physical status I or II, scheduled for elective surgery under general anesthesia. Exclusion criteria comprised BMI >30 kg/m², adrenal cortical dysfunction, neurological or psychiatric disorders, drug allergies, severe hepatic or renal impairment, severe cardiovascular disease, or recent use (within 24 hours) of analgesics, sedatives, or opioids.

Randomization 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 randomization table. Group assignments were sealed in envelopes and given sequentially to a nurse not involved in the study. Esketamine and saline were prepared in identical 20-mL syringes. Both patients and anesthesiologists were blinded to the allocation. One blinded anesthesiologist recorded haemodynamic variables and adverse effects, while another blinded anesthesiologist assessed the frequency and severity of myoclonus.

Study protocol

Routine intraoperative monitoring included pulse oximetry, ECG, and non-invasive blood pressure. A 20G intravenous cannula was inserted, and patients received oxygen at 6 L/min. Group E received 0.15 mg/kg esketamine, and Group C received an equal volume of saline, administered two minutes prior to 0.3 mg/kg etomidate given over 30 seconds. Myoclonus severity was graded as 0 (none), 1 (mild: finger or wrist movement), 2 (moderate: slight movement in one body part, e.g., face or legs), or 3 (severe: generalized or rapid limb abduction) [15]. Patients were observed for two minutes post-etomidate. Subsequently, both groups received 0.3 μg/kg sufentanil and 0.2 mg/kg cisatracurium to facilitate intubation. Anesthesia was maintained with propofol (4–6 mg/kg·h) and remifentanil (0.1–0.3 μg/kg·min) until 10 minutes before surgery completion. Mechanical ventilation targeted end-tidal CO_2 of 35–40 mmHg. Residual neuromuscular blockade was reversed with neostigmine and atropine. Hypotension (MAP <60 mmHg or <80% baseline) was treated with 6 mg ephedrine, and bradycardia (HR <45 bpm) was treated with 0.5 mg atropine.

Outcome measurements

The primary outcome was the incidence of myoclonus within two minutes of etomidate administration. Secondary outcomes included myoclonus severity, adverse events (dizziness, bradycardia, hypotension, hallucinations), and haemodynamic parameters (MAP and HR) measured at baseline (T0), five minutes after induction (T1), and five minutes after surgery initiation (T2).

Sample size calculation

Sample size estimation was performed using PASS 11 (Kaysville, UT, USA). Based on previous studies [16], a 70% incidence of myoclonus was anticipated in the control group. Assuming a 40% reduction in incidence, an alpha of 0.05, 80% power, and 10% dropout, at least 50 patients per group were required.

Statistical analysis

Data were analyzed using IBM SPSS Statistics v21. Normality was assessed with the Shapiro–Wilk test. Continuous variables were presented as mean ± SD and compared using unpaired two-tailed t-tests. Categorical data were reported as counts and analyzed with chi-squared or Fisher's exact tests. Repeated measures were analyzed with repeated measures ANOVA. A two-sided $P < 0.05$ was considered statistically significant.

Results and Discussion

Of 126 patients assessed, 100 met the inclusion criteria and were enrolled (eight declined participation, and 18 had anesthetic plan changes) **(Figure 1)**. No significant differences were observed between groups regarding age, sex, height, weight, or ASA physical status **(Table 1).**

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.

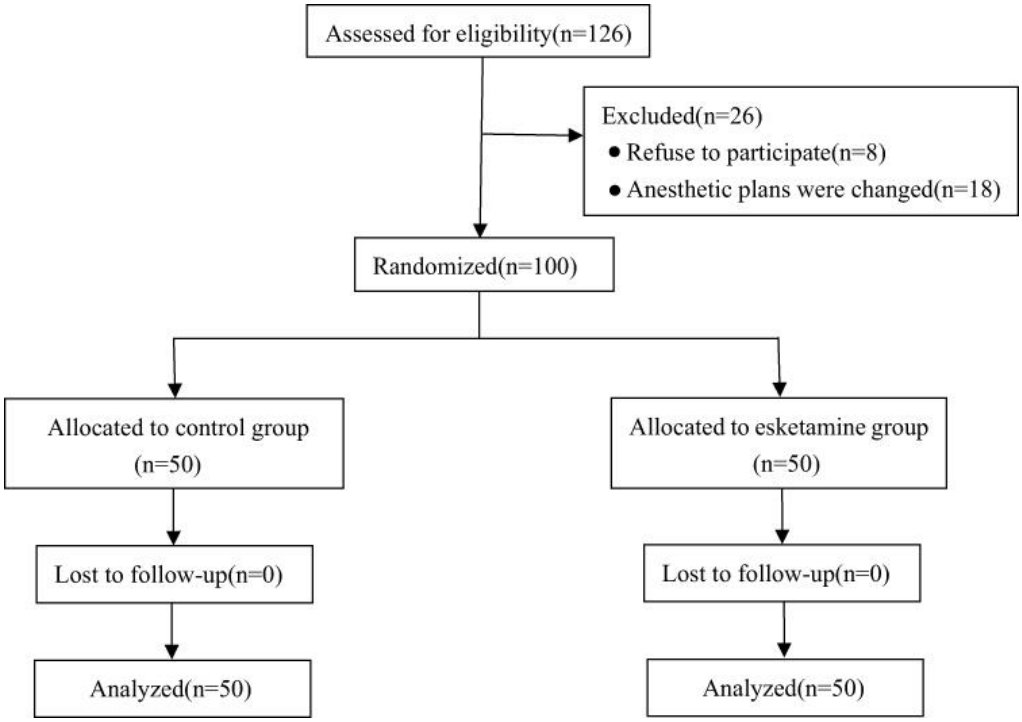

Figure 1. Study Flow Diagram.

Pretreatment with esketamine before etomidate administration led to a significant reduction in the incidence of etomidate-induced myoclonus, showing a 42% decrease (20% vs 62%, RR = 0.32, 95% CI = 0.215–0.523, P = 0.003). Group E exhibited significantly lower rates of moderate and severe myoclonus within two minutes of etomidate injection compared with Group C ($P < 0.05$). No significant difference was observed between the groups for mild myoclonus ($P > 0.05$) **(Table 2).**

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.

There were no significant differences in mean arterial pressure or heart rate between the groups at any of the three monitored time points during general anesthesia (P > 0.05) **(Tables 3 and 4).**

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.

The occurrence of dizziness, bradycardia, hypotension, and hallucinations was similar between the two groups (P > 0.05); in Group E, one patient experienced dizziness and two experienced hypotension, whereas three patients in Group C developed hypotension **(Table 5).**

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.

This study demonstrated that pretreating patients with 0.15 mg/kg esketamine before etomidate induction significantly decreased both the incidence and severity of etomidate-induced myoclonus.

Etomidate, an imidazole derivative, is widely recognized for its strong hypnotic effects and superior haemodynamic stability compared with other induction agents [17]. Nevertheless, its most notable adverse effect is myoclonus, which was observed in 62% of patients in this study. Previous research reported similar incidences: Fethi *et al*. [18] found a 66% incidence after 0.3 mg/kg etomidate administered over 20 seconds, and Abbas *et al*. [9] reported 71.8% under the same dosage and timing. Slower injection rates of etomidate have been shown to reduce myoclonus [1], which may explain the slightly lower incidence observed in the present study.

Several pharmacological interventions have been evaluated for preventing etomidate-induced myoclonus, including lidocaine, midazolam, opioids, dexmedetomidine, and ketamine. Fethi *et al*. [19] reported that 20 mg intravenous lidocaine administered 30 seconds before etomidate effectively suppressed myoclonus. Midazolam (0.015 mg/kg) given 90 seconds prior also reduced incidence [7], while remifentanil pretreatment decreased both the occurrence and severity [8]. Dexmedetomidine (0.5 μg/kg) administered before anesthesia induction similarly lowered myoclonus rates [10], and low-dose ketamine (0.5 mg/kg) one minute prior to etomidate was shown to be effective as well [11]. However, these agents can cause adverse effects such as hypotension, respiratory depression, or arrhythmias.

Esketamine, like ketamine, is a non-competitive NMDA receptor antagonist, but with fewer adverse effects and superior efficacy in sedation and analgesia [14, 20]. Prior studies indicated that 0.2 mg/kg esketamine maintains stable haemodynamics during induction [14], so a conservative dose of 0.15 mg/kg was selected for this study to minimize bias. Pretreatment with esketamine significantly reduced moderate and severe myoclonus, while mild myoclonus remained comparable between groups.

The precise mechanism of etomidate-induced myoclonus is not fully understood but is thought to involve subcortical disinhibition. High doses of etomidate may initially suppress cortical activity, thereby inhibiting subcortical control and causing myoclonic movements [19, 21]. Some studies suggest that myoclonus resembles

seizure-like activity [5, 22], and etomidate's interaction with GABA receptors in the reticular activating system may increase skeletal muscle pathway sensitivity, facilitating involuntary contractions [8]. Recent evidence indicates a neocortical origin of etomidate-induced myoclonus [23], suggesting that esketamine may exert its inhibitory effect by modulating NMDA receptor activity in the neocortex.

Several limitations should be noted. The study did not evaluate different esketamine doses, and further research is needed to determine the optimal dose for preventing myoclonus. The patient population did not fully represent those in whom etomidate is the induction agent of choice, particularly patients with haemodynamic instability. The primary outcome relied on subjective assessment, as no objective monitoring method is widely accepted. Finally, this was a single-center trial; larger multicenter studies are needed to confirm and extend these findings.

Conclusion

Pretreatment with 0.15 mg/kg esketamine before etomidate administration significantly reduced both the incidence and severity of myoclonus, indicating that a small dose of esketamine is an effective strategy to prevent etomidate-induced myoclonus during anesthesia induction.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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