e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(9); 834-841

Original Research Article

Evaluating the Comparative Efficacy of Various Dosages of Midazolam in Preventing Etomidate-Induced Myoclonus: A Hospital based Study

Archana Rani[1], YogeshNarwat[2], Gunjan Arora[3]

[1]Associate Professor, Department of Anaesthsiology and Critical Care, Al Fatah School of Medical Sciences and Research, Dhauj, Faridabad

[2]Associate Professor, Department of Anaesthesia, Al Falah School of Medical Sciences and Research Centre, Faridabad

[3]Associate Professor, Department of Anaesthesia, Al Falah School of Medical Sciences and Research Centre, Faridabad

Received: 28-06-2023 / Revised: 25-07-2023 / Accepted: 29-08-2023
Corresponding author: Dr. Gunjan Arora
Conflict of interest: Nil

Abstract:

Background: Etomidate is a commonly used induction agent in clinical practice, primarily due to its numerous advantages. These include its ability to maintain a stable hemodynamic profile without affecting the sympathetic nervous system or baroreceptors, its minimal impact on respiration, and its ability to prevent histamine release in both healthy patients as well as individuals with reactive airway disease. However, it is possible that it may be linked to myoclonus, a condition that has been observed to occur in 50% to 80% of non-premedicated individuals. Ideally, an optimal pretreatment medication for the prevention of myoclonic movements should possess characteristics such as a short duration of action, little impact on respiratory and hemodynamic functions, and absence of any adverse effects on the recovery process following anaesthesia. The use of midazolam as a pretreatment to reduce myoclonus has been investigated using various dosages, with diverse outcomes. However, the most effective dosage has yet to be determined.

Aims and Objectives: The objective of this study was to conduct a comparative analysis of the impact of three different dosages of midazolam (0.015 mg/kg, 0.03 mg/kg, and 0.05 mg/kg) in the prevention of etomidate-induced myoclonus.

Materials and Methods: The sample for this study consisted of 164 patients who were members of the American Society of Anesthesiologists I/II. These patients were between the ages of 18 and 60 and provided consent to participate in the study. The participants were allocated into four groups using a randomization process. Subsequently, the participants in group M0 received pretreatment with normal saline, while those in group M1 received a dosage of midazolam at 0.015 mg/kg. Group M2 received a dosage of midazolam at 0.03 mg/kg, and group M3 received a dosage of midazolam at 0.05 mg/kg. The main objective of the study was to determine the frequency of myoclonus occurrence following the administration of etomidate. The secondary outcome criteria were the assessment of myoclonus severity and the evaluation of alterations in hemodynamic parameters. The quantitative data was compared using a one-way analysis of variance with Bonferroni's correction. The chi-square test was utilized to analyze qualitative data. Additionally, in order to account for the numerous comparisons conducted across the four groups, Bonferroni's correction was implemented. A significance level of $P < 0.01$ was deemed appropriate for determining statistical significance.

Results: A considerable decrease in the occurrence of myoclonus was seen in group M1 when compared with group M0 ($P < 0.001$). Significant reduction in the intensity of myoclonus was detected in all three groups administered with midazolam, in contrast to the placebo group ($P < 0.001$). However, there was no significant difference observed among the patients who received varying dosages of midazolam.

Conclusion: It is recommended to provide a pretreatment of midazolam at a dosage of 0.015 mg/kg as a preventive measure against myoclonus produced by etomidate.

Keywords: Etomidate; General anesthesia; Hemodynamics; Incidence; Midazolam; Myoclonus.

Introduction

Etomidate is widely utilized as an induction agent in clinical practice because to its several advantageous properties. These include a very steady hemodynamic profile, limited release of histamine, cerebral protection, and favorable pharmacokinetics. As a result, it allows for quick recovery following administration either as a single bolus or continuous infusions. Nevertheless, there are potential adverse effects that may be linked to its usage, including injection-related discomfort, nausea and vomiting following surgery, adrenal suppression, superficial thrombophlebitis, as well as myoclonus. [1, 4, 5] The occurrence of myoclonus following the administration of etomidate has been shown to reach rates ranging from 50% to 80% in individuals who have not received premedication. [4-6]

Myoclonus is a neurological condition characterized by abrupt, rapid, and involuntary contractions of muscles, which can occur in an irregular or rhythmic pattern. The observed movements are a result of muscle contractions. [7] The potential repercussions of this unfavorable impact can be significant among certain patient populations, such as non-fasted emergency patients who face potential for regurgitation and aspiration, individuals with open globe injuries who have an elevated likelihood of vitreous material prolapse, and patients who have poor cardiovascular reserve due to the enhanced myocardial oxygen consumption resulting from these muscle contractions. [1, 2]

Several pharmaceutical agents have been investigated for their potential efficacy in mitigating the symptoms of myoclonus. The substances encompassed under this list consist of magnesium sulphate, fentanyl, remifentanil, dexmedetomidine, a minimal dose of etomidate administered prior to a hypnotic dosage, diazepam, and midazolam. [1, 8-11]

Midazolam emerges as a favorable option because to its brief duration of action and little impact on ventilation and hemodynamics when administered within commonly prescribed dosage ranges. Various dosages have been provided in order to decrease the occurrence of etomidate-induced myoclonus, yielding diverse outcomes. Different researchers have experimented with dosage ranges spanning from 0.015 mg/kg up to 0.05 mg/kg. [9, 11]

Nevertheless, there is a gap in the current pool of research pertaining to the establishment of a standardized dosage for the mitigation of myoclonus. Consequently, the current study was designed to investigate the impact of various dosages of midazolam (namely, 0.015 mg/kg, 0.03 mg/kg, and 0.05 mg/kg) for the prevention of etomidate-induced myoclonus.

Aims and Objectives

The objective of this study was to evaluate and compare the impact of three different dosages of midazolam (0.015 mg/kg, 0.03 mg/kg, and 0.05 mg/kg) on the prevention of etomidate-induced myoclonus.

Materials and Methods

Following the approval of the institutional ethics committee, research employing a randomized, double-blind, placebo-controlled design was carried out within the Department of Anaesthesia & Critical Care at a teaching hospital specializing in tertiary care in North India.

The research involved a sample of 164 ASA I/II patients, who had given their consent. These patients were between the ages of 18 and 60 and were scheduled to have elective surgical operations that required general anaesthesia. The study excluded individuals who had a medical history indicating potential neuropsychological or neuromuscular illness, adrenal cortical dysfunction, allergy to midazolam, epilepsy, recent use of any kind of analgesic or sedative within the past 24 hours, as well as pregnant or lactating women.

The participants were allocated into four groups of 41 individuals each by a computer-generated random number table, employing a randomization process. Allocation concealment was achieved by use sealed opaque envelopes. The test medicine was formulated by an individual who was not affiliated with the study, and both the participant and the investigator conducting the study were unaware of the group assignment, thereby ensuring blinding.

In this study, the patients were administered different pretreatment interventions based on their assigned groups. Group M0 got pretreatment with normal saline, group M1 received midazolam at a dosage of 0.015 mg/kg, group M2 received midazolam at a dosage of 0.03 mg/kg, and group M3 received midazolam at a dosage of 0.05 mg/kg. The total volume of the administered pretreatment in all groups was 5 ml. All patients were administered a 0.5 mg tablet of Alprazolam on the evening preceding the surgical procedure. However, no premedication was administered on the day of the surgery. In the operating room, following the application of standard monitoring devices, an 18-gauge intravenous catheter was placed and a Ringer's lactate infusion was initiated. The experimental medication was administered through injection for duration of 30 seconds. Subse-

quently, at a time interval of ninety seconds, a dose of etomidate measuring 0.3 mg/kg was administered intravenously over duration of twenty seconds. The patient had a 60-second observation period, after which the administration of vecuronium & morphine took place. Tracheal intubation was subsequently conducted after a 3-minute interval.

The occurrence of myoclonus persisted following the delivery of vecuronium, as a subset of individuals exhibited myoclonus after a time interval of 60 seconds had passed. The study involved the monitoring of several physiological parameters, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (SPO2).

These measurements were taken at regular one-minute intervals both before and after the administration of the test medication. Additionally, measurements were taken following the injection of etomidate and continued until five minutes after intubation. The beginning of the experiment was indicated by the time point labeled as 0 minutes, which coincided with the delivery of the test medication, namely the injection of etomidate. The subsequent readings were taken at 2 minutes after etomidate administration, 3 minutes after the administration of vecuronium, and at the 6-minute time point following intubation. Therefore, the hemodynamic parameters were seen to be influenced by tracheal intubation starting from 6 minutes onwards.

The clinical grading system for myoclonus intensity consisted of four levels: 0 indicating the absence of myoclonus, 1 representing mild myoclonus characterized by slight fasciculation limited to the face and/or distal upper and/or lower extremities, 2 denoting moderate myoclonus characterized by pronounced movements of the face and/or limbs, and 3 indicating severe myoclonus involving both the limbs and trunk. [9] The main objective of the study was to determine the incidence of myoclonic movements following the administration of etomidate. The secondary outcome variables encompassed the assessment of myoclonus severity subsequent to etomidate injection, the evaluation of changes in heart rate (HR) and mean arterial pressure (MAP) following the administration of the test medication, etomidate, and intubation, as well as the determination of the occurrence of airway challenges such as laryngospasm and bronchospasm.

Sample Size Calculation

Based on a placebo group incidence rate of 70% for myoclonus and a clinically meaningful decrease of 50%, with $\alpha = 0.05$ & $\beta = 0.2$, the determined sample number was 31 individuals in each of the groups. [10] However, within the context of the suggested four groups, three comparisons were made between each group and the control group. Consequently, the Bonferroni correction was employed to determine statistical significance. Considering this revision, a total of 41 patients were included in each group for the study.

Statistical Analysis

The statistical analysis was conducted using SPSS version 20. The study employed a one-way analysis of variance (ANOVA) with Bonferroni's correction to assess and compare quantitative data related to demographic profiles and hemodynamic parameters. The chi-square test was utilized to compare qualitative data, namely the gender ratio, ASA physical rating, and the incidence & severity of myoclonus across several groups. A significance level of $P < 0.05$ was deemed to indicate statistical significance. Additionally, in order to account for the numerous comparisons conducted across the four groups, Bonferroni's correction was implemented. A significance level of $P < 0.01$ was deemed appropriate to determine statistical significance.

Results

Out of the total of 188 individuals evaluated for being eligible, 166 patients fulfilled the criteria for inclusion. Two participants declined to give their consent, resulting in a total of 164 individuals being enrolled in the study.

A total of 164 patients were allocated into four groups, with each group consisting of 41 patients. The allocation was performed using a computer-generated random number table. The demographic characteristics of the four groups were similar, with the exception of the gender distribution. Female patients made up a larger portion of the study's total population. [Table 1].

Table 1: Demographic data

Variables	Group M0	Group M1	Group M2	Group M3	P- Value
Age (years)	34.51±12.51	31.71±9.41	31.91±9.91	34.21±11.21	0.499
Gender (M:F)	16:25	9:32	22:19	11:30	0.014
Weight (kg)	60.21±10.81	54.71±12.71	54.71±13.51	59.61±13.11	0.077
ASA (I:II)	35:6	34:7	37:4	29:12	0.0122

The incidence of myoclonus was found in the patients following the administration of etomidate across all four groups. The observed discrepancy in the occurrence was found to be statistically significant, with a p-value <0.001. Group M1 exhibited a significant decrease in the occurrence of myoclonus in comparison to group M0. The statistical analysis comparing M1 and M0 yielded a significant result ($p < 0.001$). There were no statistically significant differences seen among the four groups (M0 vs. M2, $P = 0.108$, & M0 vs. M3, $P = 0.014$) ($P > 0.01$). [Table 2]

Table 2: Incidence of Myoclonus

Groups	N (%)	Significance (Bonferroni)	P- Value
M0	35 (85.4)		<0.001
M1	18 (43.9)	M0 vs. M1	<0.001
M2	29 (70.7)	M0 vs. M2	<0.108
M3	25 (61.0)	M0 vs. M3	<0.014

A statistically significant decrease in the severity of myoclonus was found in the three groups administered midazolam, as compared with the placebo group ($P<0.001$). There were no notable disparities observed in the severity of myoclonus among the patients who were administered varying dosages of midazolam.

Given the larger clinical relevance of moderate or severe myoclonus in comparison to mild myoclonus, individuals exhibiting moderate-to-severe myoclonus were categorized as a single group and contrasted with those displaying mild or no myoclonus. Group M0 exhibited a statistically significant increase in the prevalence of patients experiencing moderate-to-severe myoclonus when compared with all three of the midazolam groups (M0 vs. M1: $P < 0.001$; M0 vs. M2: $P = 0.001$ and M0 vs. M3: $P = 0.001$).

There were no statistically significant variations seen in the occurrence of moderate-to-severe myoclonus compared to mild or absence of myoclonus across the various dosages of midazolam administered to the patients ($P > 0.01$). [Table 3]

Table 3: Severity of Myoclonus

Myoclonus grade	M0 N (%)	M1 N (%)	M2 N (%)	M3 N (%)	P- Value
0 (None)	5 (12.5)	23 (56.1)	12 (29.3)	15 (36.6)	<0.001
1 (Mild)	2 (4.9)	6 (14.6)	8 (19.5)	5 (12.2)	
2 (Moderate)	8 (19.5)	4 (9.8)	9 (22.0)	9 (22.0)	
3 (Severe)	26 (63.4)	8 (19.5)	12 (29.3)	12 (29.3)	
2 + 3	34	12	21	21	<0.001
0 + 1	07	29	20	20	

The four groups exhibited similar hemodynamic characteristics prior to the surgical procedure (baseline). [Table 4] The mean arterial blood pressure exhibited similar values among the groups following the administration of the test medication, subsequent to the administration of etomidate, and up to 5 minutes after intubation. There were no instances of airway complications, such as laryngospasm or bronchospasm that were detected.

Table 4: Hemodynamic parameters

Parameters	Group M0	Group M1	Group M2	Group M3	P- Value
HR (bpm)	89.31±13.1	89.41±19.10	88.61±16.71	90.31±16.21	0.977
SBP (mmHg)	131.61±11.51	124.61±14.71	124.61±13.51	127.61±12.81	0.055
DBP (mmHg)	82.51±7.61	78.21±9.41	78.81±8.71	79.11±8.51	0.096
MAP (mmHg)	98.91±7.61	93.61±10.31	94.11±9.41	95.21±9.21	0.044

Discussion

A notable decrease in the occurrence of myoclonus was seen in group M1 in comparison to group M0. The study saw a notable decrease in the severity of myoclonus across all three groups receiving midazolam, with a higher proportion of patients in the control group experiencing moderate-to-severe myoclonus. Nevertheless, there were no observed variations in the frequency and intensity of myoclonus across the three groups administered with midazolam.

Etomidate is recognized for its distinctive capacity to maintain hemodynamic stability, low impact on respiratory function, and provision of cerebral protection. Nevertheless, it is possible that there is a correlation between this phenomenon and the negative impact of myoclonus, prompting the investigation of various pharmaceutical interventions aimed at

mitgating its effects. The pharmacological agents utilized in this context encompass a range of substances, in-cluding butorphanol, [2,10] fentanyl,[4,10] lignocaine,[5] magnesium sulphate, [9] remifentanil,[9,12] sufentanil,[13] dexmedetomidine, [14,15] propofol, [16] gabapentin, [17] oxycodone, [18] ketamine, [19] etomidate (administered in a low dosage before to the hypnotic dose), [11,20,21] and midazolam. [4,9,15,22-25]

Midazolam is considered a favorable pharmacological medication for the prevention of myoclonic movements, mostly due to its brief duration of action and limited notable systemic effects. [26] Various investigations in the existing literature have employed midazolam at dosages spanning from 0.015 mg/kg up to 0.05 mg/kg. Nevertheless, the ideal dosage of this medication as a preliminary measure to reduce the severity of muscle spasms has yet to be determined. This emphasizes the necessity for more randomized controlled studies that involve bigger and more reliable sample sizes [23]. In our investigation, the observed occurrence rate of myoclonus in the absence of midazolam pretreatment was found to be 85%. A number of further investigations have documented the presence of myoclonic activity in a range of 50% to 80% among individuals who have been administered etomidate.[10,11]

The relationship between myoclonic movement and several parameters, including the age of the patient, gender, dosage of etomidate, and the rate of etomidate injection, has been demonstrated in previous studies. [20, 26, 27]. The age of the patients in our investigation was consistent across all four groups, thereby ruling out age as a contributing factor to the disparity in myoclonus occurrence. Research studies have indicated that there is a greater prevalence of myoclonus among male patients in comparison to their female counterparts.[27] The observed increased frequency of men in group M2 in our study relative to females may perhaps explain the greatest prevalence of myoclonus (71%) seen in this group. The incidence of myoclonus can be influenced by the dosage and rate of administration of etomidate. The researchers, Wasinwong et al., reported an elevated occurrence of myoclonus as the dosage of etomidate dose. [22] The administration of etomidate at a slower injection rate of 2 minutes, in contrast to a faster rate of 10-20 seconds, has been linked to a reduction in the occurrence of myoclonus. [22-27]. The use of the usual dosage of etomidate administered as a bolus during a 20-second period may have had a role in the elevated occurrence of myoclonus noticed in the placebo group of the current investigation, accounting for 85% of cases.

The time interval between the completion of the test drug used for pretreatment for myoclonus attenuation & the subsequent administration of etomidate is an additional distinguishing element among various investigations. In the current investigation, a time interval of 90 seconds was utilized. However, previous research has shown varying durations for this interval, varying between 2-4 minutes. [4, 9, 22, 25] Therefore, it is plausible to suggest that had we extended the waiting period to duration beyond 90 seconds, the observed outcomes may have potentially diverged.

In the current investigation, the occurrence of myoclonus following pretreatment with midazolam at a dosage of 0.015 mg/kg was seen to be around 44%. This incidence demonstrated a statistically significant decrease in comparison to the control group. Numerous prior research documented a notably greater prevalence of myoclonus compared to our study when employing this specific dosage of midazolam. [9, 13, 15] In their respective studies, Sedighinejad et al. [9] and Dey and Kumar [15] observed an incidence rate of 71.85% & 62.5% after midazolam was given 2 minutes prior to anaesthesia induction. Sedighinejad et al.'s [9] study did not have a control group, which they cited as a drawback.

The researchers conducted a comparative analysis of the effects of midazolam at a dosage of 0.015 mg/kg in relation to magnesium sulphate, remifentanil, and low-dose etomidate in order to evaluate the occurrence of myoclonus during a period of 90 seconds. The administration of a low dosage of etomidate before to therapy was seen to have a notable impact on both the frequency and intensity of myoclonus.

In a study conducted by Dey and Kumar [15], the authors examined the effects of midazolam at a dosage of 0.015 mg/kg and dexmedetomidine at a dosage of 0.5 μg/kg. Notably, the study did not include a control group. Both medications were provided as infusions over a period of 10 minutes prior to the induction of anaesthesia using etomidate. This study demonstrated that dexmedetomidine had more efficacies in mitigating myoclonus compared to midazolam. Nevertheless, there was a disparity in the rate of administration between our study and the study in question, with midazolam 0.015 mg/kg being administered over duration of 10 minutes in their case, as opposed to the 20 seconds utilized in our study. In a study conducted by Alipour et al. [13], it was shown that the incidence of myoclonus was much greater, reaching 84%, in patients who received pretreatment with midazolam at a dosage of 0.015 mg/kg, and subsequent induction after 90 seconds with etomidate at a dosage of 0.3 mg/kg. Nonetheless, a notable con-

straint of their study was the comparatively reduced sample size of 25, in contrast to our study which encompassed a larger sample of 41 participants.

However, a study conducted by Hüter et al. [24] found that administering a pretreatment of 0.015 mg/kg midazolam 90 seconds before anaesthesia induction using 0.3 mg/kg etomidate in patients having elective cardioversion resulted in a notable decrease in the occurrence of myoclonus when compared with the control group. Specifically, the myoclonus frequency was reduced to 10% in the treatment group, whereas it remained at 50% in the control group. The disparity in the occurrence rate of myoclonus between our study and the referenced study (10% vs. 44%) might perhaps be attributed to the administration of magnesium therapy in both cohorts. Furthermore, it is important to note that the patient cohort examined in the present study differed from our own, since it only consisted of older individuals classified as ASA III or IV. Furthermore, it should be noted that the sample size employed in their study was quite limited.

In recent comparative research [11], the effectiveness of midazolam (0.015 mg/kg) and low-dose etomidate (0.03 mg/kg) as pretreatment agents to determine the occurrence of myoclonus during etomidate induction was examined. The study's findings indicated that the midazolam group exhibited a reduced frequency and severity of myoclonus. This observation aligns with our findings, which indicate that the occurrence of myoclonus was lowest (44%) in the cohort that received a dosage of 0.015 mg/kg of midazolam.

In our investigation, the administration of a pretreatment dose of 0.03 mg/kg of midazolam resulted in an incidence of myoclonus of around 71%. The observed value in the control group was comparatively lower, however it did not reach a level of statistical significance. The findings of our study align with those of Isitemiz et al. [4], which demonstrated that administering midazolam at a dosage of 0.03 mg/kg before inducing anaesthesia with etomidate at a dosage of 0.3 mg/kg led to myoclonus in 70% of patients, compared with 85% in the control group. However, this difference was not statistically significant. Wasinwong et al. [22] given a comparable dosage and observed a myoclonic movement incidence rate of 78% in their study.

In the current investigation, the occurrence of myoclonus was noted in 61% of the participants who had a pretreatment of midazolam at a dosage of 0.05 mg/kg. The findings of our study differ from those of Malay et al. [28] and Aktolga et al. [29], who observed a myoclonus incidence of 40% & 37%, respectively, while administering a comparable dosage. The discrepancy in the occurrence of myoclonus between our study and the aforementioned research may be ascribed to the disparity in the dosage of etomidate supplied. Specifically, the other studies utilized a dosage that was just adequate to induce a loss of eyelid reflex, whilst we administered a complete induction dosage of 0.3 mg/kg.

Therefore, in the current investigation, the administration of midazolam at three different dosages, specifically 0.015 mg/kg, 0.03 mg/kg, and 0.05 mg/kg, prior to the administration of etomidate at a dose of 0.3 mg/kg, resulted in a reduction in the occurrence of myoclonic movements. Nevertheless, a notable reduction was observed just in the group with a dosage of 0.015 mg/kg. The hemodynamic variables were intact and similar across all groups at different time intervals, indicating the safety of administering three doses of midazolam.

The myoclonus severity was dramatically decreased when treated with any of the three dosages of midazolam, in comparison to pretreatment with normal saline.

Nevertheless, there were no notable disparities observed among the various dosages of midazolam. No notable problems were seen during the research period in relation to the administration of midazolam.

Limitations of the study

In the present research, the patients were classified into ASA I/II groups, which are not considered optimal for the administration of etomidate for use as an induction drug. Furthermore, the monitoring of anaesthesia depth was not feasible during the induction phase.

Conclusion

In conclusion, the administration of midazolam pretreatment at dosages of 0.015 mg/kg, 0.03 mg/kg, and 0.05 mg/kg prior to the induction of anaesthesia with etomidate at a dose of 0.3 mg/kg has been found to considerably diminish the severity of myoclonus. Nonetheless, a noteworthy decrease in the occurrence of myoclonus was found exclusively at a dosage of 0.015 mg/kg.

The current study did not find any significant benefits associated with larger doses of midazolam, namely 0.03 mg/kg and 0.05 mg/kg, compared to the lower dose of 0.015 mg/kg. Therefore, we suggest utilizing a midazolam pretreatment dose of 0.015 mg/kg as a preventive measure against etomidate-induced myoclonus.

Financial support and sponsorship: Nil.

References

1. Luan HF, Zhao ZB, Feng JY, Cui JZ, Zhang XB, Zhu P, et al Prevention of etomidate-induced myoclonus during anesthetic induction by pretreatment with dexmedetomidine Braz J Med Biol Res. 2015;48:186–90.
2. Zhao X, Bao R, Zhu J, Liu Z, Meng Y, Fan X, et al., Pretreatment with butorphanol reduces myoclonus after etomidate J Anesthesiol Clin Sci. 2013;2:2.
3. Soleimanpour H, Safari S, Rahmani F, Jafari Rouhi A, Alavian SM. Intravenous hypnotic regimens in patients with liver disease; a review article Anesth Pain Med. 2015;5: e23923.
4. Isitemiz I, Uzman S, Toptaş M, Vahapoglu A, Gül YG, Inal FY, et al Prevention of etomidate-induced myoclonus: Which is superior: Fentanyl, midazolam, or a combination? A retrospective comparative study Med Sci Monit. 2014; 20:262–7.
5. Safavi M, Honarmand A, Sahaf AS, Sahaf SM, Attari M, Payandeh M, et al Magnesium sulfate versus Lidocaine pretreatment for prevention of pain on etomidate injection: A randomized, double-blinded placebo-controlled trial J Res Pharm Pract. 2015; 4:4–8.
6. Ko BJ, Oh JN, Lee JH, Choi SR, Lee SC, Chung CJ. Comparison of effects of fentanyl and remifentanil on hemodynamic response to endotracheal intubation and myoclonus in elderly patients with etomidate induction Korean J Anesthesiol. 2013; 64:12–8.
7. 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 Wkly. 2014;144: w14042.
8. Bruder EA, Ball IM, Ridi S, Pickett W, Hohl C. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients Cochrane Database Syst Rev. 2015;1:CD010225.
9. Sedighinejad A, Naderi Nabi B, Haghighi M, Biazar G, Imantalab V, Rimaz S, et al Comparison of the effects of low-dose midazolam, magnesium sulfate, remifentanil and low-dose etomidate on prevention of etomidate-induced myoclonus in orthopedic surgeries Anesth Pain Med. 2016;6:e35333.
10. Kewalramani A, Choudhary S, Kushwaha R, Sharma NP, Bhateja S. Comparison of butorphanol with fentanyl for reducing etomidate-induced myoclonus: A prospective, randomised clinical trial Indian J Clin Anaesth. 2016; 3:329–33.
11. Nazemroaya B, Mousavi SM. Comparison of premedication with low-dose midazolam versus etomidate for reduction of etomidate-induced myoclonus during general anesthesia for electroconvulsive therapy: A randomized clinical trial Anesth Pain Med. 2019;9: e94388.
12. Hwang JY, Kim JH, Oh AY, Do SH, Jeon YT, Han SH. A comparison of midazolam with remifentanil for the prevention of myoclonic movements following etomidate injection J Int Med Res. 2008; 36:17–22.
13. Alipour M, Tabari M, Azad AM. Comparative study evaluating efficacy of sufentanil versus midazolam in preventing myoclonic movements following etomidate J Anaesthesiol Clin Pharmacol. 2016; 32:29–32.
14. Du X, Zhou C, Pan L, Li C. Effect of dexmedetomidine in preventing etomidate-induced myoclonus: A meta-analysis Drug Des DevelTher. 2017; 11:365–70.
15. Dey S, Kumar M. Comparison of pretreatment with dexmedetomidine with midazolam for prevention of etomidate-induced myoclonus and attenuation of stress response at intubation: A randomized controlled study J Anaesthesiol Clin Pharmacol. 2018; 34:94–8.
16. Liu J, Liu R, Meng C, Cai Z, Dai X, Deng C, et al Propofol decreases etomidate-related myoclonus in gastroscopy Medicine (Baltimore). 2017;96: e7212.
17. YılmazÇakirgöz M, Demirel İ, Duran E, Özer AB, Hancı V, Türkmen ÜA, et al Effect of gabapentin pretreatment on myoclonus after etomidate: a randomized, double-blind, placebo-controlled study Revista Brasileira de Anestesiologia. 2016; 66:356–62.
18. Wang W, Lv J, Wang Q, Yang L, Yu W. Oxycodone for prevention of etomidate-induced myoclonus: A randomized double-blind controlled trial J Int Med Res. 2018;46:1839–45.
19. Wu GN, Xu HJ, Liu FF, 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 (Baltimore). 2016;95: e2701.
20. Mullick P, Talwar V, Aggarwal S, Prakash S, Pawar M. Comparison of priming versus slow injection for reducing etomidate-induced myoclonus: A randomized controlled study Korean J Anesthesiol. 2018; 71:305–10.
21. Nyman Y, von Hofsten K, Ritzmo C, Eksborg S, Lönnqvist PA. Effect of a small priming dose on myoclonic movements after intravenous anaesthesia induction with Etomidate-Lipuro in children Br J Anaesth. 2011; 107:225–8.
22. Wasinwong W, Uakritdathikar T, Kovitwanawong N, Pakam P. Prevention of etomidate-

induced myoclonic movement after midazolam co-induction with low-dose etomidate Songklanagarind Med J. 2011;29:1–9.
23. Zhou C, Zhu Y, Liu Z, Ruan L. Effect of pre-treatment with midazolam on etomidate-induced myoclonus: A meta-analysis J Int Med Res. 2017;45:399–406.
24. Hüter L, Schreiber T, Gugel M, Schwarzkopf K. Low-dose intravenous midazolam reduces etomidate-induced myoclonus: A prospective, randomized study in patients undergoing elective cardioversion AnesthAnalg. 2007; 105:1298–302.
25. Kwon MS, Kim JH, Baik HJ. The effect of midazolam for reducing myoclonus after etomidate Korean J Anesthesiol. 2002; 43:395–400.
26. Giffin JP, Cottrell JE, Shwiry B, Hartung J, Epstein J, Lim K. Intracranial pressure, mean arterial pressure, and heart rate following midazolam or thiopental in humans with brain tumors Anesthesiology. 1984; 60:491–4.
27. Do SH, Han SH, Park SH, Kim JH, Hwang JY, Son IS, et al The effect of injection rate on etomidate-induced myoclonus Korean J Anesthesiol. 2008; 55:305–7.
28. Malay PH, Rajesh C, Monal RN, Seema G. A comparison of dexmedetomidine and midazolam for the prevention of myoclonic movements and pain following etomidate injection Res J Pharm Biol Chem Sci. 2015; 6:161–8.
29. Aktolga S, Gunes Y, Gunduz M, Isik G. A comparison of midazolam and dexmedetomidine for the prevention of myoclonic movements and pain following etomidate injection J Anaesth Clin Pharmacol. 2010; 26:162–6.