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Investigating the effect of ondansetron in reducing myoclonic movements caused by intravenous administration of etomidate

Mohammad Alipour[1] and Seyed Javad Purafzali Firuzabadi[1*]

Abstract

Background Etomidate is a short-acting intravenous anesthetic used to induce general anesthesia. However, myoclonus caused by the administration of etomidate is seen in 50–80% of untreated patients. Due to the high prevalence of myoclonus following etomidate injection, the present study aimed to investigate the effect of ondansetron in reducing myoclonic movements caused by the intravenous administration of etomidate.

Method The current research was a double-blind clinical study conducted on 72 adult patients who were candidates for elective eye surgery and had visited Khatam Al-Anbia Eye Hospital affiliated to Mashhad University of Medical Sciences between November to December 2022. Before sampling, the designed proposal was approved by the Ethics Committee of Mashhad University of Medical Sciences and clinical trial was registered by the code IRCT20190510043545N2 at 2021-10-02. Candidate patients for elective eye surgery with ASA class I-II were selected using the available sampling method. Prior to study entrance the study protocol was fully explained and an informed constant was obtained from each participant. The patients were randomly assigned into two groups; 4 mg (IV) ondansetron was prescribed for the study group and 5 cc of normal saline (IV) was administered for the placebo group. The mentioned drugs were administered as a pre-medication 180 s before etomidate induction with a dosage of 0.3 mg/kg. After examining and recording the induced myoclonus, a full dose of narcotics and muscle relaxants was prescribed for each patient.

Results Each group consisted of 36 patients who did not differ significantly in terms of age, gender, comorbidities and ASA class. The mean time of myoclonus in the placebo and ondansetron groups was 43.48 ± 53.17 and 14.07 ± 5.75, respectively, which was significantly shorter in the ondansetron group ($Z=-5.19$, $P<0.005$). The severity ($\chi 2=14.62$, $P<0.005$) and incidence ($\chi 2=25.89$, $P<0.005$) of myoclonus were also significantly lower in the ondansetron group compared to placebo.

Conclusion The administration of ondansetron in combination with etomidate can have a remarkable effect on reducing the duration and severity of myoclonus induced by etomidate.

Keywords Ondansetron, Myoclonus, Etomidate

*Correspondence:
Seyed Javad Purafzali Firuzabadi
Sjvdpurafzali@yahoo.com
[1]Department of Anesthesiology and Critical Care, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction

Etomidate is a short-acting intravenous anesthetic used to induce general anesthesia. This drug is one of the carboxylated derivatives of imidazole, which weakens the function of the central nervous system by strengthening the effect of the gamma-aminobutyric acid (GABA) neurotransmitters [1].

Etomidate is an aminobutyric acid (GABA) ligand receptor that suppresses the reticular activating system in the central nervous system [2] and since it causes few changes in the hemodynamic status of patients, it is considered a desirable drug. However, myoclonus is a complication that still challenges anesthesiologists [3].

Etomidate- induced myoclonus is seen in 50–80% of untreated patients, which ranges from fine movements in the fingers to severe clonic movements [2]. Involuntary movements caused by etomidate administration may lead to muscle damage, myalgia, hyperkalemia, and the accidental displacement of vascular access and control devices [3]. The administration of etomidate in patients with open-globe injury, full stomach, high blood pressure, coronary artery disease and intracranial aneurysm is dangerous [2, 3].

Although many drugs have been tested to reduce the amount of myoclonic activity after etomidate administration, the neural mechanism of etomidate-induced myoclonus is unclear [2]. Narcotics effectively reduce myoclonic movements; However, their application may lead to side effects such as respiratory depression, apnea, stiffness in the chest wall, nausea and vomiting. Therefore, when administering such drugs, the advantages and disadvantages should be considered [4].

Due to the high prevalence of myoclonus following etomidate injection, various studies have been conducted to reduce and control this complication. In this regard, it is preferable to use drugs that cause the least complications. The effects of midazolam pretreatment, propofol, dexmedetomidine and butorphanol on etomidate-induced myoclonus have been investigated in a number of clinical trials [5–7].

Ondansetron is a selective antagonist agent for the 5-hydroxytryptamine 3 receptor and is very effective in the treatment and prevention of nausea and vomiting [8]. Moreover, the effectiveness of this drug as an HT-5 receptor antagonist has been investigated in the prevention of shivering after coronary artery bypass grafting with a pump [9]. Its effect on GABA receptors is one of the possible reasons for the effectiveness of ondansetron in reducing etomidate-induced myoclonus. Considering the possible effect of this drug on the incidence of myoclonus and the lack of studies in this regard, the present study was conducted with the aim of investigating the effect of ondansetron in reducing myoclonic movements caused by the intravenous administration of etomidate.

Materials and methods

This double-blind clinical trial study was conducted on 72 adult patients who were candidates for elective eye surgery and referred to Khatam Al-Anbia Eye Hospital affiliated to Mashhad University of Medical Sciences between November to December 2022. Before sampling, the designed proposal was approved by the ethics committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1400.234) and the clinical trial was registered by the code IRCT20190510043545N2 at 2021-10-02 (https://irct.behdasht.gov.ir/trial/58661). Prior to study entrance the study protocol was fully explained and an informed consent was obtained from each participant.

Inclusion and exclusion criteria

Patients over the age of 18 years, with a body mass index (BMI) in the normal range and ASA class I or II undergoing elective eye surgery under anesthesia were included in this study. Cases with a history of a neurological disease, muscle disorders, adrenal cortex dysfunction, pregnancy or breastfeeding, having an underlying disease, a history of allergic reaction to ondansetron, and those having received painkillers or sedatives in the last 24 h were excluded from the study.

Determining the sample size:

Given an alpha 0.05 and beta 0.20 (80% power), and considering the incidence of myoclonus at a rate of 75% in the control group [10] and 40% in study group, the sample size was calculated as 30 subjects in each group.

Study plan

The present study was conducted on 72 adult patients who were candidates for elective eye surgery with ASA I-II, and had undergone general anesthesia. The desired sample was selected using the available sampling method.

Upon entering the operating room, the patient's fasting state was checked, a full medical history including information of co-morbidities was obtained, then a peripheral vein was taken. Standard monitoring, including electrocardiography, pulse oximetry, and non-invasive blood pressure (NIBP) was performed at 3-minute intervals for all patients. Patients were randomly (using the block method) assigned to two groups: ondansetron with the dosage of 4 mg (IV) was injected for the study group and 5 cc normal saline (IV) was injected for the placebo group, both as a prodrug 180 s before 0.3 mg/kg etomidate induction.

After evaluating the myoclonus caused by etomidate, the patient was prescribed a full dose of narcotic drug (fentanyl 1 μg/kg), muscle relaxant (atracurium 0.5 mg/kg) and a suitable airway was established for the patient.

Myoclonus was classified based on the following grading system:

mild = (small movements of a part of the body such as a finger or wrist).

moderate = (gentle movements of 2 different muscle groups such as face and legs).

severe= (severe clonic movements in 2 or more muscle groups or rapid limb adduction).

In this study, the presence, severity, and duration of myoclonus were considered as primary outcomes, while the association between age, gender, ASA class, and myoclonus was examined as secondary outcomes.

Both the data collector and data analyst were unaware of the patients' group.

At the end, the obtained data were analyzed by the SPSS software version 23. Kolmogorov-Smirnov test was used to check the normal distribution of the collected data. In order to compare the two groups, t-test was used, and in case of non-parametric data, Mann-Whitney was applied. Qualitative variables were examined by chi-square test and the correlation test was used to examine the relationship between the studied variables. The significance level was set at $P < 0.05$.

Results

In total, 72 patients were enrolled in this double-blind clinical trial. The subjects were divided into two groups (36 patients each) (Fig. 1). Demographic data of the patients along with ASA class, and their medical history are presented in Table 1 indicating no statistically significant difference between the two groups in term of these variables ($P > 0.005$).

The mean Myoclonus duration was 53.17 ± 43.48 and 5.75 ± 14.07 s in the placebo and *Ondan*setron groups,

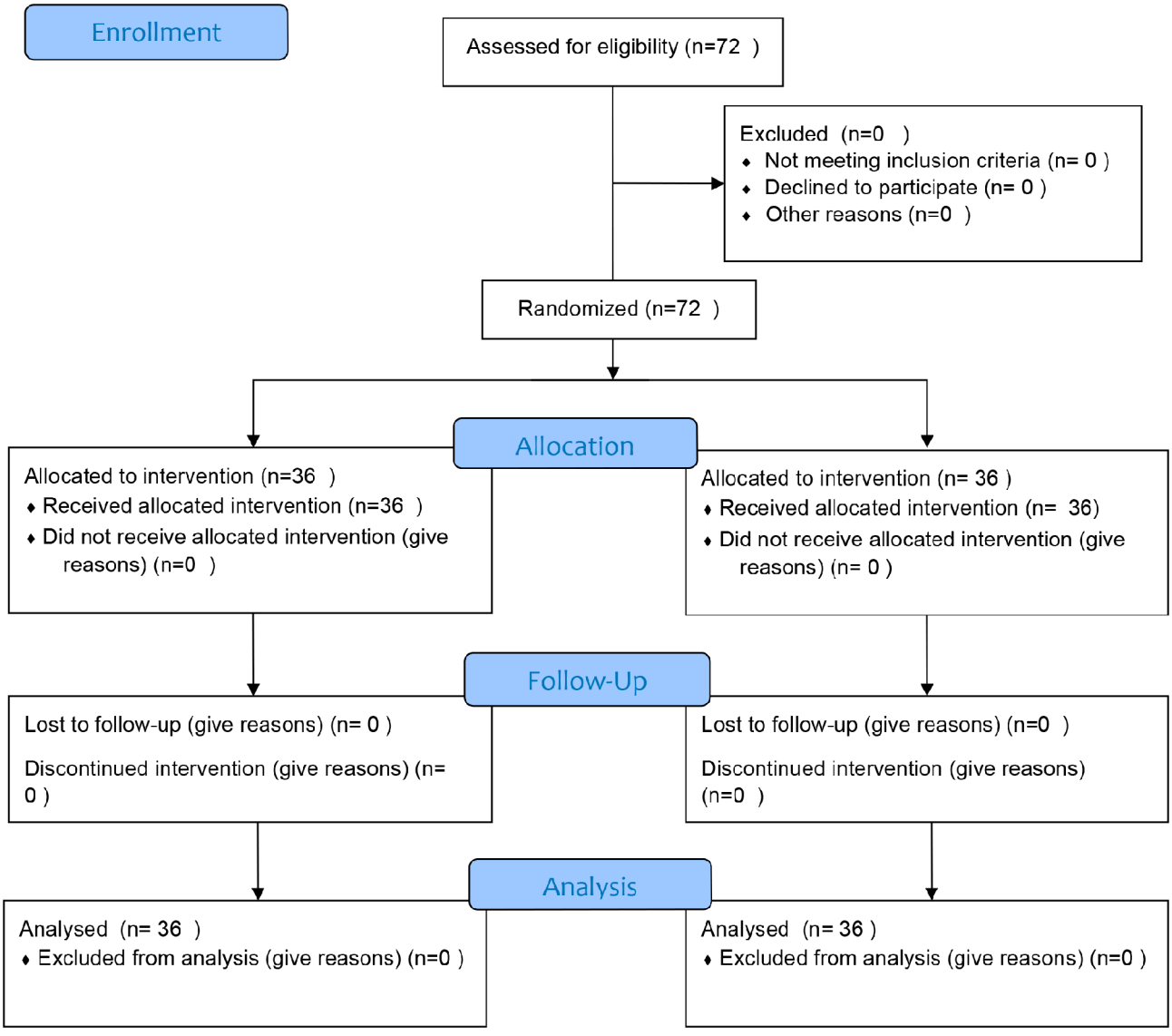

Fig. 1 Consort flow diagram of participants in two groups of the study

Table 1 The demographic data of the patients in the placebo and Ondansetron groups

Variables		Placebo		Ondansetron		Total		t–test	*P*-value
		Mean	SD	Mean	SD	Mean	SD		
Age		56.12	18.43	52.81	19.91	59.44	16.44	1.28	0.26
Categorized variables		No	Percent	No	Percent	No	Percent	χ^2	P-value
Gender	Male	14	38.9	15	41.7	29	40.3	0.05	0.81
	Female	22	61.1	21	58.3	43	59.7		
ASA[1] class	1	22	61.1	23	63.9	45	62.5	2.06	0.35
	2	14	39.9	13	36.1	25	34.7		
Diabetes mellitus	yes	3	8.3	4	11.1	7	9.7	0.15	0.69
	no	33	91.7	32	88.9	65	90.3		
Ischemic heart disease	yes	4	11.1	1	2.8	5	6.9	1.93	0.16
	no	32	88.9	35	97.2	67	93.1		
Hypertension	yes	8	22.2	11	30.6	19	26.4	0.64	0.42
	no	28	77.8	25	69.4	53	73.6		
Hypothyroidism	yes	1	2.8	0	0	1	1.4	1.01	0.31
	no	35	97.2	36	100	71	98.6		
Hyperthyroidism	yes	0	0	0	0	0	0	-	-
	no	36	100	36	100	72	100		
Hyperlipidemia	yes	0	0	0	0	0	0	-	-
	no	36	100	36	100	72	100		

[1] American Society of Anesthesiologists Classification

Table 2 Comparison of the presence and severity of myoclonus in the two groups

Variables	Myoclonus	Placebo		*Ondan*setron		Total	
		No	Percent	No	Percent	No	Percent
Presence of Myoclonus	Yes	29	80.6	13	36.1	42	58.3
	No	7	19.4	23	63.9	30	41.7
Severity of Myoclonus	Mild	4	11.1	8	22.2	12	16.7
	Moderate	7	19.4	4	11.1	11	15.3
	Severe	18	50.0	1	2.8	19	26.4

respectively, accordingly the myoclonus duration was shorter in the *Ondan*setron group compared to placebo. This duration was significantly shorter in patients receiving *Ondan*setron in comparison to placebo (Z=-5.19, $P<0.005$). The presence and severity of myoclonus after intravenous injection of placebo *and ondan*setron in the two groups is presented in Table 2. Myoclonus was significantly more common in the placebo group compared to the *Ondan*setron group ($\chi^2=14.62$, $P<0.005$). Moreover, the comparison of the severity of myoclonus showed a significant difference between the two groups, being less in the *ondan*setron group in comparison to placebo ($\chi^2=25.89$, $P<0.005$).

The mean value of vital signs before and after intervention in the two groups are displayed in Table 3. Based on the obtained results, there was no significant difference between the two groups in terms of systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation and heart rate before the intervention ($P>0.005$). In addition, no significant difference in vital signs was observed between the two groups after the intervention ($P>0.005$).

We also compared the vital signs before and after the intervention separately in each group. Based on the obtained results, no significant difference was reported in terms of diastolic blood pressure and heart rate ($P>0.005$); whereas a significant difference was observed in systolic blood pressure, oxygen saturation, and mean arterial pressure ($P<0.005$) before and after the intervention in the placebo plus etomidate group. Nevertheless, a significant difference in all vital signs was obtained before and after the intervention in the etomidate plus *ondan*setron group ($P>0.005$), except for heart rate ($P>0.005$).

No correlation was achieved between age (r=-0.17; $P=0.13$) and gender ($r=0.05$; $P=0.66$) with the presence of myoclonus. In this regard, the incidence of myoclonus was not related to aging or gender. Moreover, no correlation was observed between ASA class and the incidence of myoclonus (r=-0.06; $P=0.57$). The relationship between the presence and severity of myoclonus with the patients' medical history is displayed in Table 4. Based on the obtained results, there was no correlation between the presence, severity, and duration of myoclonus with the patient's medical history ($P>0.005$).

Table 3 The mean value of vital signs before and after intervention in two groups

Variables	Before intervention						Statistical analysis	*P*-value	After intervention						Statistical analysis	*P*-value
	Placebo		Ondansetron		Total				Placebo		Ondansetron		Total			
	Mean	SD	Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD		
Systolic blood pressure(mmHg)	150.67	27.68	148.78	21.66	149.72	24.69	-0.01	0.99	134.36	28.77	136.14	22.09	135.25	25.48	2.15	0.14
Diastolic blood pressure(mmHg)	87.78	11.01	89.06	12.01	88.42	11.46	-0.41	0.68	83.83	17.42	83.28	13.71	83.56	15.57	-0.44	0.66
Mean arterial pressure	109.17	16.8	110.58	17.06	109.88	16.83	-0.49	0.62	100.86	21.27	99.36	16.8	100.11	19.04	-0.11	0.91
Pulse oximetry saturation (%)	97.25	1.73	96.75	2.156	97	1.957	-0.78	0.43	98.81	1.546	98.19	1.99	98.50	1.8	-1.65	0.09
Heart rate	80.31	16.61	83.25	17.58	81.78	17.05	0.15	0.69	82.03	16.76	80.28	17.3	81.15	16.94	0.07	0.78

When considering the correlation between age and the severity of myoclonus, the myoclonus severity increased with aging (r=-0.28; P = 0.01). However, no correlation was observed between age and severity of myoclonus when each of the two groups was investigated separately (placebo: r=-0.3; P = 0.07, *ondan*setron: r=-0.21; P = 0.21).

Discussion

The findings of the present study showed that the duration of myoclonus was shorter in patients receiving ondansetron along with etomidate compared to those receiving placebo and etomidate. The incidence and intensity of myoclonus was also lower in the ondansetron group compared to placebo. Furthermore, no correlation was observed between age, gender, ASA class and medical history of patients with the occurrence of myoclonus. The severity of myoclonus increased with age, however, no correlation was observed with the other aforementioned factors.

To date, various drugs have been investigated to prevent the heterogeneity of brain activity caused by etomidate in order to control the centers responsible for the development of myoclonus. Propofol, ketamine and etomidate are among these drugs, each of which have specific side effects. In this regard, the multiple advantages of etomidate, such as speed of action, cardiovascular stability with minimal respiratory side effects, and intracranial pressure protection, have introduced it as an ideal back agent for rapid induction, especially for patients with an unstable hemodynamic status [11]. Etomidate active GABA receptors that suppresses the reticular activating system of the central nervous system. Although many drugs have been tested to reduce the amount of myoclonic activity after etomidate administration, the neural mechanism of etomidate-induced myoclonus is unclear. Nevertheless, this drug has side effects including pain during injection and the risk of myoclonus occurrence [12].

Etomidate-induced myoclonus seems to be the result of impaired subcortical inhibition. The use of etomidate can lead to a decreased activity of the cerebral cortex [13, 14].

Etomidate suppresses the activation system of the central nervous system by interacting with GABA receptors. Dysfunction of GABA neurons increases the sensitivity of pathways related to skeletal muscle control. These events eventually lead to myoclonic muscle contractions [15].

Most related studies on the present issue have focused on the comparison of etomidate with a control group and have mainly emphasized on the benefits of prescribing etomidate during anesthesia induction compared to its non-application [12, 13].

According to the findings of a meta-analysis, the incidence and severity of myoclonus caused by etomidate

Table 4 The correlation between the patients' medical history with presence, severity and duration of myoclonus

Patients' medical history	Presence of Myoclonus		Severity of Myoclonus		Myoclonus duration	
	R	*P*-value	*R*	*P*-value	*R*	*P*-value
Diabetes mellitus	-0.08	0.46	-0.05	0.65	-0.02	0.81
Ischemic heart disease	-0.12	0.31	-0.04	0.69	-0.05	0.67
Hypertension	0.13	0.26	0.15	0.19	0.16	0.16
Hypothyroidism	0.14	0.23	0.12	0.29	0.12	0.29

injection in patients treated with midazolam was lower than the control group [5]. Accordingly, in 2019, a double-blind clinical trial by Nazemroaya et al. investigated the effect of pretreatment with low-dose midazolam in reducing myoclonus caused by etiomidate. In this study, the patients were divided into three groups receiving midazolam (0.015 mg), etomidate (0.03 mg) and placebo. The findings indicated a lower frequency of myoclonic movements in the midazolam group compared to the placebo and etomidate groups. However, the intensity of myoclonic movements was higher in the midazolam group compared to the other two groups. Vital signs, seizures' duration, recovery time and the occurrence of apnea were also evaluated; except for the duration of seizures, which was shorter in the midazolam group, no difference was observed between the two groups [16].

In a similar study by Hüter et al., midazolam 0.015 mg/kg was administered to patients with selective cardioversion for 90 s before induction of anesthesia with etomidate, and the results showed a decrease in myoclonic movements [17]. These findings have been confirmed by Wazinwong, Hwang, Zhou and Alipour studies [5, 18–20]. Other studies having used higher doses of midazolam, also further confirmed the aforementioned effects [17, 19]. In the study by Nazemroaya et al., the dosage used was different from that of other studies and myoclonus was reported in 24% of the patients. However, in other studies having used a similar dose, the rate of myoclonus varied and was reported between 10 and 60% [17–20].

In general, the efficacy of midazolam in controlling etiomidate-induced myoclonus has been confirmed. However, in order to prevent the side effects caused by midazolam such as reduced level of consciousness and apnea, it is very important to use drugs with fewer side effects. In our study, ondansetron was introduced as a suitable drug for controlling etiomidate-induced myoclonus.

To date, no study has investigated the effect of ondansetron on etomidate-induced myoclonus. However, some studies have focused on the effects of this drug on other side effects similar to that of etomidate, such as shivering after anesthesia. Postoperative hypothermia and shivering are frequent and unpleasant side effects of general and local anesthesia [21]. Prevention and treatment of post-anesthesia shivering is an important aspect of patient care, as it may be associated with a number of harmful consequences, including increased oxygen consumption and carbon dioxide production. Shivering may lead to increase in metabolic activity, increased oxygen uptake up to 100% and arterial hypoxia, which are associated with an increased risk of myocardial ischemia [22]. Inhibition of the HT3-5 system leads to a dose-dependent reduction in shivering. Ondansetron is a specific HT3-5 receptor antagonist [15]. The mechanism of action of this drug can be related to inhibition of serotonin in the preoptic area of the anterior hypothalamus [9]. In this regard, a double-blind randomized clinical trial was conducted with the aim of comparing the effectiveness of ondansetron and meperidine on 90 patients undergoing general anesthesia; the results indicated the effectiveness of ondansetron versus meperidine in preventing post-operative shivering. There was no difference in the amount of myoclonus, seizures and rashes between the two groups [11]. Similarly, Kelsaka et al. study has supported the effect of ondansetron on preventing post-operative shivering [9]. However, the results of another study indicated that ondansetron does not respond to the shivering threshold. The difference in the results of these studies can be due to the different dosage of the prescribed drug used [9, 24].

The effectiveness of different anesthetic drugs on etomidate-induced myoclonus has been investigated in various studies. Rapid induction without any complications is an ideal feature. Both etomidate and propofol enable rapid induction [23]. Propofol is the most common intravenous anesthetic drug which its low dose (0.25 to 0.75 mg per kg) effect has been confirmed in reducing etomidate-induced myoclonus by several studies [15, 24].

Due to the hemodynamic stability and minimal respiratory reduction in patients receiving etomidate, this drug has a wider safety margin than barbiturates or propofol [25]. Although the use of narcotics is effective in reducing postoperative pain and myoclonus, the use of these drugs in addition to propofol increases the risk of prolonged apnea [25, 26], decreases arterial blood pressure, and also increases the incidence of nausea and vomiting [18]. By increasing the dose of propofol, the incidence of side effects such as respiratory inhibition and blood pressure drop, increases [27].

Low-dose ketamine has also shown its efficacy in preventing painful myoclonus [11]. Although the

neural mechanism of etomidate-induced myoclonus is unknown, some studies have shown that myoclonus activity may be associated with N-methyl-D-aspartate seizures. Ketamine acts by blocking glutamatergic neurotransmission through N-methyl-D-aspartate (NMDA) receptors [11, 28]. Also, pre-administration of low-dose ketamine is useful in improving intubation status and postoperative analgesia management [29, 30]. The study of Hoyer et al. confirmed the superiority of ketamine over etomidate in terms of seizure duration [31].

Other studies have shown that lidocaine (20 mg) and thiopental (0.1 mg/kg) can also reduce myoclonus [32, 33]. In addition, gabapentin (800 and 1200 mg) can reduce the frequency and severity of myoclonic movements associated with etiomidate [34].

Among myoclonus-controlling drugs, pretreatment with narcotics is the most effective method [4]. Opioid receptors activation can inhibit seizures. A meta-analysis was conducted to investigate the effect of pretreatment with narcotics on etomidate-induced myoclonus prevention. It showed that the use of narcotics leads to a reduction in myoclonic movements [35]. Zhang et al. found no difference between midazolam and butorphanol (a narcotic) in controlling myoclonic movements, but their combined treatment had superior effects [36]. Another study showed that the incidence of myoclonus after pretreatment with fentanyl 100, 250 and 500 µg intravenously 5 min before anesthesia induction with etomidate was 33, 13 and 0%, respectively, but the prevalence of apnea increased up to 87, 87 and 100%, respectively [37]. Furthermore, cough, chest wall stiffness and apnea have been observed in patients treated with fentanyl [38, 39]. In general, high doses of opioids (fentanyl, sufentanil, and remifentanil) effectively reduce myoclonic movements, but are associated with adverse side effects such as cough, apnea, respiratory depression, and chest wall stiffness [4].

Nevertheless, some studies have investigated the effectiveness of sedative drugs on etomidate-induced myoclonus. Some drugs, such as dezocin, mainly bind to opioid k-receptors and modulate them. A clinical trial showed the incidence of myoclonus decrease to zero after using dezocin. However, some patients in the dezocin group complained of dizziness or nausea [40]. The findings of a meta-analysis indicated that pre-injection of dezocin reduces the incidence of myoclonus and its severity, but does not affect dizziness, nausea and heart rate [41]. Levan et al. estimated the prevalence of myoclonus in patients who received 0.5 and 1 mg of dexmedetomidine to be 30 and 36%, which was significantly reduced compared to the isotonic saline group (63%) [42]. these findings were also confirmed by Du et al. [43].

Several factors reduce etomidate-related myoclonus to different degrees. However, the exact mechanism of etomidate-induced reduction of myoclonus is unclear. It has been hypothesized that myoclonic activity may be associated with disinhibition of subcortical structures due to inhibition at the level of the spinal cord or cerebral cortex, instead of being associated with epilepsy [15, 17].

Limitations

The present study was the first to investigate the effect of ondansetron in reducing myoclonic movements caused by the intravenous administration of etomidate. However, this study had certain limitations, including not investigating the dose-dependent effect of ondansetron and comparing it with other drugs of this category, such as granisetron. Therefore, further studies are recommended focusing on the dose-dependent effect of ondansetron in etomidate-induced myoclonus.

Conclusion

The intravenous administration of ondansetron (4 mg) as a prodrug 180 s before etomidate injection can reduce the duration and severity of etomidate-induced myoclonus.

Abbreviations

IV	Intra Venous
GABA	Gamma-aminobutyric acid
BMI	Body mass index
NMDA	N-methyl-D-aspartate

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Author contributions

Mohammad Alipour: design of the work, interpretation of data, substantively revised the work and approved the submitted version Seyed Javad Purafzali Firuzabadi: design of the work, analysis, interpretation of data, drafted the work or substantively revised it and approved the submitted version.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The proposed study plan was approved by the ethics committee of Mashhad University of Medical Sciences. (IR.MUMS.MEDICAL.REC.1400.234). Prior to study entrance the study protocol was fully explained and an informed consent was obtained from each participant. The participants were assured that all information will remain confidential.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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