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CLINICAL & BASIC RESEARCH

Efficacy of Granisetron versus Sufentanil on Reducing Myoclonic Movements Following Etomidate

Double-blind, randomised clinical trial

Mohammad Alipour,[1] Naeem Abdi,[2] *Parisa Zaj,[1] Leila Mashhadi[1]

abstract: ***Objectives:*** This study aimed to reduce the intensity of myoclonus movements by comparing the effectiveness of granisetron and sufentanil in reducing the intensity of etomidate-induced myoclonic movements. Etomidate-induced myoclonus occurs in up to 85% of patients under general anaesthesia. This type of myoclonus can induce significant clinical and economic problems in patients with special conditions. ***Methods:*** This double-blind randomised clinical trial study consisted of 96 adult patients recruited between January and July 2021 from Mashhad University of Medical Sciences, Mashhad, Iran. Using block randomisation, subjects were divided into three groups of 32 patients: the group receiving granisetron 40 µg/kg (group G), the group receiving sufentanil 0.2 µg/kg (group S) and the control group who did not receive the pretreatment (group C). Patients received these medications as pretreatments 120 seconds before induction with etomidate. After the injection of etomidate with a dose of 0.3 mg/kg, the incidence of myoclonus was evaluated. After evaluating the myoclonus, the full dose of narcotics (fentanyl 1 µg/kg) and muscle relaxants (atracurium 0.5 mg/kg) were administered to patients and a suitable airway was established for them. ***Results:*** The findings indicated that granisetron reduced the intensity and incidence of myoclonic movements more than sufentanil. In addition, myoclonic movements were observed at a significantly higher intensity in the control group (P = 0.001). ***Conclusion:*** The results obtained from the current study indicate that granisetron and sufentanil as pretreatments are effective for reducing myoclonus in patients.

Keywords: Granisetron; Sufentanil; Etomidate; Myoclonus; Movement; Iran.

Advances in Knowledge

- *This study helped the authors obtain more data and knowledge about the efficacy of granisetron and sufentanil as well as their effect on quality of anaesthesia and recovery after surgery.*
- *Both granisetron and sufentanil show very promising results in reducing myoclonic movements during induction of anaesthesia.*

Applications to Patient Care

- *Regarding the use of granisetron and sufentanil in controlling and reducing myoclonic movements during general anaesthesia, it can be effective in improving the quality of anaesthesia in case of its use in the hospital.*

Etomidate is an intravenous general anesthetic agent, whose clinical effects are developed through enhancing the gamma-aminobutyric acid inhibitory system by altering chloride conduction.[1] Due to its rapid induction of anaesthesia with minimal changes in cardiovascular function, it is one of the most widely used intravenous anaesthetics in patients with limited cardiorespiratory function.[1,2] It is derived from imidazole and may cause pain as well as myoclonus in patients during and after injection.[3] Etomidate injection pain is minimised by applying fat emulsions in etomidate compounds, but myoclonus caused by etomidate is still a clinical challenge.[4] Myoclonus refers to sudden, brief twitching or jerking as well as shock-like involuntary movements of a muscle or group of muscles.[5,6] Myoclonus caused by etomidate occurs in up to 85% of patients under anaesthesia.[5] It begins in a limited part of the body and spreads to muscles in other areas. Myoclonus can cause many significant problems in more severe cases, such as ventilation disturbance.[5,6] Electrophysiological studies are useful in evaluating myoclonus, not only for confirming the clinical diagnosis but also for understanding the underlying physiological mechanisms. Since the majority of myoclonic jerks are believed to be caused by the hyperexcitability of a group of neurons in certain cerebral structures, the relationship of myoclonic jerks with electroencephalogram activity is of primary importance in the study of myoclonus.[7,8]

Different drugs (fentanyl, remifentanil, midazolam, etc.) have been used as pretreatment for myoclonus caused by etomidate, each with exclusive side effects, while the best option for clinical treatment of etomidate-induced myoclonus has not yet been determined.[9–12] Fentanyl is a single synthetic opiate

[1]Department of Anesthesiology, Mashhad University of Medical Sciences, Mashhad, Iran; [2]Student Research Committee, School of Nursing and Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran
*Corresponding Author's e-mail: parisazaj66@yahoo.com

used for analgesia. Today, fentanyl is widely used for anaesthesia and pain relief. Among the side effects of this drug are itching and impaired breathing.[5,9] As an opioid analgesic, sufentanil is an analogue of fentanyl and is used to induce as well as maintain anaesthesia plus postoperative analgesia. In practice, it seems that the hemodynamic stability of sufentanil anaesthesia during surgery is better than that of other opioids or inhaled anesthesia.[13,14] The side effects of sufentanil include hypotension and impaired respiration.[14,15] The effect of sufentanil pretreatment on myoclonus caused by etomidate has been studied by many researchers who have published different results. According to a study in 2003, the incidence of etomidate-induced myoclonus in patients receiving sufentanil as a pretreatment was zero.[15] According to another study in 2016, the incidence of etomidate-induced myoclonus with sufentanil pretreatment was 28%.[16]

Granisetron is one of the serotonin receptor antagonists used as an anti-nausea and vomiting drug in surgeries, chemotherapy, etc.[17] This drug has minor side effects and may cause constipation, headaches and confusion in people who are allergic to the drug.[17] The effect of granisetron on etomidate-induced myoclonus has not been studied yet. However, the efficacy of granisetron was investigated as a pretreatment on propofol-induced myoclonus in a previous study.[18] It showed that the incidence of propofol-induced myoclonus with granisetron was only 5.5% and most of the patients (94.5%) experienced myoclonic movements with grade 0 (without myoclonus).[18] Since myoclonus induced by etomidate injection in certain patients can have significant side effects, this study was conducted for the first time to determine the effectiveness of granisetron on the intensity of myoclonus induced by intravenous administration of etomidate and to compare it with sufentanil.

Methods

This double-blind clinical trial study was performed on selected patients referred to educational hospitals affiliated with the Mashhad University of Medical Sciences, Mashhad, Iran, from January to July 2021. In this study, 96 patients were selected via convenience sampling and based on a table of random numbers generated by a computer. After that, based on random blocks and in parallel, they were divided into two intervention groups (granisetron and sufentanil groups) plus a control group with 32 subjects each.

Inclusion criteria were patients undergoing general anaesthesia with: (1) the American Society of Anesthesiologists (ASA) classification I and II; and (2) aged between 15 and 60 years. Exclusion criteria included: (1) adrenal dysfunction; (2) history of allergy to opioid analgesics and hypnotics drugs; (3) mental disorders; (4) neuromuscular diseases; (5) seizures; (6) electrolyte imbalance; (7) history of addiction; (8) long QT syndrome, as well as severe cardiovascular diseases; (9) high intracranial pressure and intraocular pressure; and (10) increased intra-abdominal pressure.

Patients underwent isotonic intravenous fluid therapy at 5mL/kg for 10 minutes before induction. Further, standard monitoring, including pulse oximetry, electrocardiogram, non-invasive blood pressure and capnography, was performed on them. Patients were randomly (block randomisation) assigned into three groups of granisetron (group G 40 μg/kg), sufentanil (group S 0.2 μg/kg) and control group (group C). First, the studied drugs with a volume of 5 mL were administered within 30 seconds. Then, after 120 seconds, etomidate was injected at a dose of 0.3 mg/kg for 30 seconds. The incidence and intensity of myoclonus were evaluated by a person who was not aware of the group allocations (anaesthesia resident) 120 seconds after the administration of etomidate. The drugs were injected by an anaesthetist who was unaware of the type of drugs.

In this double-blind study, the intensity of myoclonus was measured with a score between zero and three, where zero represents no myoclonus, one indicates mild—small movements of a part of the body such as finger or wrist, two denotes moderate—gentle movements of two different muscle groups such as face and legs and three indicates severe—severe clonic movements in two or more muscle groups or rapid limb adduction. Thereafter, the three groups were compared with each other.[16,19] After evaluating myoclonus, the patient was prescribed a full dose of a narcotic drug (fentanyl 1 microgram/kg), a muscle relaxant (atracurium 0.5 mg/kg) and a suitable airway was established for the patient. No pretreatment was injected before etomidate administration in the control group. Sixty seconds before and after injection of each drug under study (sufentanil and granisetron), heart rate, systolic and diastolic blood pressure and arterial oxygen pressure were measured and recorded. According to the patient's vital signs, fentanyl was injected as needed in all three groups. Given that fentanyl was administered after completion of the study, it did not affect the study process. All of the administered drugs had been produced by Abu Reihan Company in Iran.

All patients were visited by an anesthesiologist for 24 hours after surgery, and their clinical condition was assessed. Confounding variables were controlled according to the control group and random assignment of samples. Using the formula of comparing a

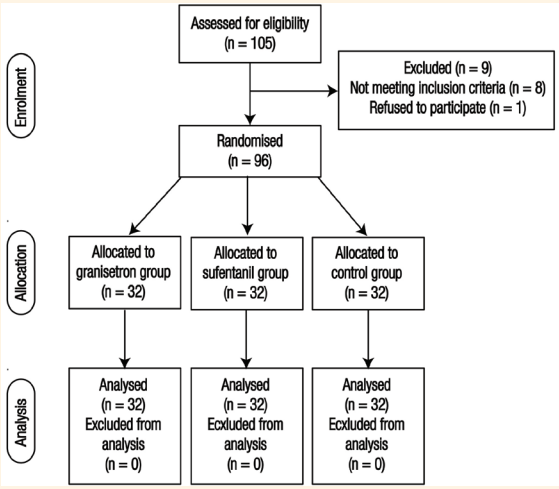

Figure 1: The consort flow diagram.

Table 1: Underlying diseases and demographic variables in the experimental and control groups (N = 96)

Variable	n (%)			Value	*P* value
	Granisetron group (n = 32)	Sufentanil group (n = 32)	Control group (n = 32)		
Gender					
Male	15 (46.9)	12 (37.5)	15 (46.9)	3.28	0.19
Female	17 (53.1)	20 (62.5)	17 (53.1)		
ASA class					
ASA I	21 (65/50)	26 (81/3)	22 (68/8)	2.16	0.33
ASA II	11 (34/50)	6 (18/3)	10 (31/2)		
HTN					
Yes	3 (9.4)	5 (15.6)	5 (15.6)	0.70	0.71
No	29 (90.6)	27 (84.4)	27 (84.4)		
Hypothyroidism					
Yes	1 (3.1)	5 (15.6)	2 (6.2)	3.54	0.17
No	31 (96.9)	27 (84.4)	30 (93.8)		
Hyperthyroidism					
Yes	1 (3.1)	0 (0.0)	0 (0.0)	2.02	0.36
No	31 (96.9)	32 (100.0)	32 (100.0)		
Diabetes					
Yes	4 (12.5)	7 (21.9)	4 (12.5)	1.42	0.42
No	28 (87.5)	25 (78.1)	28 (87.5)		
IHD					
Yes	1 (3.1)	2 (6.2)	3 (9.4)	1.06	0.58
No	31 (96.9)	30 (93.8)	29 (90.6)		
Height in cm ± SD*	172.50 ± 4.62	171.62 ± 5.67	172.69 ± 5.16	5.87	0.82
Weight in kg ± SD*	73.68 ±3.84	72.50 ± 4.13	72.40 ± 3.89	6.45	0.89
BMI ± SD*	24.49 ± 1.51	24.41 ± 2.46	24.52 ± 2.25	0.89	0.92

ASA = American Society of Anaesthesiologists; HTN = hypertension; IHD = ischemic heart disease; BMI = body mass index; SD = standard deviation.

**Height, weight and BMI are expressed as mean ± standard deviation. Other variables are expressed as frequency and percent.*

Table 2: Comparison of haemodynamic variables of patients in three groups 60 seconds before and after injection of studied drugs (N = 96)

Variable*	Mean ± SD			Value	*P* value
	Granisetron group	Sufentanil group	Control group		
Systolic I	135.00 ± 20.85	133.84 ± 23.18	128.25 ± 23.86	0.81	0.44
Diastolic I	92.81 ± 16.22	90.13 ± 17.18	87.78 ± 14.16	0.80	0.45
Systolic II	133.75 ± 20.81	125.41 ± 16.54	124.50 ± 22.61	6.63	0.48
Diastolic II	91.94 ± 15.84	81.77 ± 13.56	85.88 ± 13.63	3.97	0.22
HR I	8.4 ± 19.9	89.25 ± 13.98	90.21 ± 13.42	12.11	0.18
HR II	86.19 ± 13.96	87.63 ± 11.02	88.66 ± 11.62	11.31	0.20
SPO2 I	99.84 ± 0.51	99.53 ± 0.80	99.72 ± 0.52	0.79	0.14
SPO2 II	99.91 ± 0.29	99.98 ± 0.12	99.94 ± 0.25	0.94	0.20

SD = standard deviation; HR= heart rate; SPO2 = saturation of peripheral oxygen.

**Haemodynamic variables recorded and measured 60 seconds before injection are marked with the Roman numeral I, and variables recorded 60 seconds after injection of the studied drugs are marked with the Roman numeral II.*

Table 3: The intensity and incidence of myoclonus in the experimental and control groups after injection of etomidate (N = 96)

Variable	n (%)			*P* value
	Granisetron group (n = 32)	Sufentanil group (n = 32)	Control group (n = 32)	
0 = without myoclonus	30 (93.75)	25 (78.12)	3 (9.37)	0.001
1 = mild (small movements of a part of the body such as a finger or wrist)	2 (6.25)	5 (15.62)	20 (62.50)	
2 = moderate (gentle movements of 2 different muscle groups such as face and legs)	0 (0.00)	2 (6.26)	7 (21.88)	
3 = severe (severe clonic movements in 2 or more muscle groups or rapid limb adduction)	0 (0.00)	0 (0.00)	2 (6.25)	

qualitative trait in two communities and taking into account the findings of a previous study, that reported the incidence of grade zero myoclonus in sufentanil recipients as 72% and the clinical estimate of this index as 35% in granisetron recipients, taking into account the 5% alpha error and 80% power, the sample size in each group was equal to 29 people, which increased to 32 in each group after calculating a dropout of 10%.[16]

This study used descriptive statistical tests and Chi-squared as non-parametric tests for qualitative demographic variables and incidence of myoclonus. In addition, an analysis of variance (ANOVA) was performed to compare the mean of quantitative variables between groups using the statistical package for the social sciences (SPSS), Version 19 (IBM Coporation, Armonk, New York, USA).

The study obtained ethics approval from the Medical Ethics Committee of Mashhad University of Medical Sciences (code: IR.MUMS.MEDICAL.REC.1399.509) and registration at the Iranian Clinical Trial Center (#IRCT20210221050436N1), before beginning sampling and data collection. Written consent was obtained from all subjects and they were assured that all their information would remain confidential. In addition, at any time and even after giving consent, they could withdraw from the study voluntarily [Figure 1].

Results

From a total of 96 patients, the mean and standard deviation of the age variable in the three groups of sufentanil (S), granisetron (G) and control (C) were 39.25 ± 1.53, 39.25 ± 12.03 and 38.63 ± 10.61, respectively. According to the ANOVA test, no significant difference was observed among the three groups in terms of age variables ($P = 0.96$). The results of this study revealed that the three groups were not significantly different in terms of demographic characteristics such as gender, anaesthesia class (ASA) and underlying diseases (hypothyroidism and hyperthyroidism, hypertension, diabetes and ischaemia) based on the Chi-squared test. Other important demographic characteristics were height,

weight and BMI (body mass index). According to the ANOVA test, the mean and standard deviation of these variables did not differ significantly between the three groups [Table 1]. In this study, patients' haemodynamic status was monitored and recorded based on the variables of systolic and diastolic blood pressure, heart rate and arterial oxygen pressure 60 seconds before and after the injection of the studied drugs. The study results based on ANOVA statistical test indicated that there was no significant difference between the three groups [Table 2]. According to the main objective of the present study, one of the most important variables was the intensity of etomidate-induced myoclonic movements. Patients in the granisetron group showed less intensity of myoclonic movements relative to the sufentanil and control groups based on the Chi-squared test. However, in the control group, these movements were measured and recorded with more intensity and created a statistically significant difference from the other two groups [Table 3].

Discussion

The major advantage of etomidate is its stable cardiovascular profile, which aids in counteracting the sympathetic stress response during laryngoscopy and intubation.[20] Despite all benefits of this drug, myoclonus is still a significant side-effect.[16,21] The main mechanism of myoclonus caused by etomidate is unknown. However, one hypothetical mechanism for etomidate-induced myoclonus is that high concentrations of etomidate suppress cortical activity earlier than subcortical function. For this reason, the extent and severity of myoclonus can be reduced through pretreatments that inhibit the excitatory activity of the subcortical region.[16,19–21] The use of various drugs such as dexmedetomidine, opioids, benzodiazepines, lidocaine, magnesium sulfate, muscle relaxants and gabapentin as pretreatment agents to reduce myoclonus induced by etomidate injection has been investigated.[20–25] However, the drugs offered should be limited to specific and exact cases. It is important to choose an optimal agent as a pretreatment in relation to the type and duration of surgery as well as the patient's condition. Accordingly, this double-blind study was performed to evaluate the effect of granisetron and sufentanil on reducing the intensity of myoclonic movements following etomidate injection as a pretreatment in comparison with the control group.

One of the differences between this study compared to similar works was investigating the effectiveness of granisetron, which had not been studied before. The efficacy of granisetron was investigated as a pretreatment in a previous study, showing that the incidence of propofol-induced myoclonus with granisetron was only 5.5% and most of the patients (94.5%) experienced myoclonic movements with grade zero (without myoclonus).[18] The results of the present study are in line with the previous study and a significant reduction has been observed in the intensity and incidence of myoclonus movements. Although the functional mechanism of granisetron in reducing myoclonus movements is not clear yet, it can be introduced as a new and valuable pretreatment. The sufentanil group also experienced less intensity and incidence of myoclonic movements compared to the control group, and the results of this study confirm its effectiveness. Numerous studies have shown that narcotics effectively reduce the intensity of myoclonus movements, though they may come at the cost of respiratory depression, apnea, nausea and vomiting.[26,27] Nyman *et al*. demonstrated that pretreatment with 100 mg of fentanyl reduced the incidence of myoclonus by up to 8%.[28] In addition, another study demonstrated that higher doses of fentanyl (500 μg) significantly reduced myoclonic movements. However, the incidence of apnea increased during induction.[29] A study by Kelsaka *et al*. demonstrated that remifentanil injection (1μg/kg) 120 seconds minutes before the etomidate injection reduced myoclonic movements by up to 7% without any clinical changes.[30] In many studies, it has been demonstrated that sufentanil (0.3 μg/kg) is an effective pretreatment in reducing the intensity of myoclonic movements induced by etomidate injection.[15] In a study by Alipour *et al*., the effectiveness of sufentanil (0.2 μg/kg) in reducing the intensity and duration of myoclonic movements was also confirmed, which was consistent with the present study.[16] A study by Feng *et al*. clarified that etomidate increased the mean behavioural scores and glutamate levels in the cerebrospinal fluid plus neocortex during anaesthesia.[31] More importantly, they demonstrated a strong correlation between the myoclonus and neocortical glutamate accumulation. In that study, the authors concluded that etomidate-induced myoclonus was associated with neocortical glutamate accumulation. Suppression of the astrogliosis in the neocortex and promotion of extracellular glutamate uptake by regulating glutamate transporters in the motor cortex may be the therapeutic target for preventing etomidate-induced myoclonus.[31] Accordingly, it can be postulated that the action of granisetron in reducing myoclonic movements is the above mechanism, though it needs more investigations, especially in terms of pharmaceutical, cellular and

molecular properties. In general, different outcomes may depend on several factors and may be partly due to the dose as well as the timing of pretreatment agents along with the different conditions of patients. The findings of the present study regarding the reduction of the intensity of myoclonic movements due to the pretreatment of sufentanil are in line with the results of other studies. However, the pretreatment effect of granisetron significantly reduced myoclonus induced by etomidate injection compared to placebo, making it even superior to sufentanil.

In past studies, it has been stated that myoclonus can cause important clinical complications, but whether these complications cause permanent damage or not has not been proven and is debatable.

One of the most important limitations of this study was the lack of previous studies on the use and effectiveness of granisetron as a pretreatment in reducing myoclonic movements. This made the mechanism of action of granisetron for reducing myoclonic movements unclear. Thus, it is recommended to conduct larger studies with more samples and different doses of granisetron. Another limitation was that, although authors refer to it as a blinded study, blinding was a nonformal 'observer blinded' approach.

Conclusion

Overall, the study results suggest that granisetron is similar to sufentanil and even more effective in reducing the intensity of myoclonic movements following etomidate's injection and can be an important step in the development of further studies in this field. It is recommended that further studies be performed to compare granisetron with other pretreatment agents in the future.

AUTHORS' CONTRIBUTION

MA, NA, PZ and LM conceptualised and designed the research. PZ, MA and LM were responsible for sampling and intervention. NA was responsible for statistical analysis. PZ and MA drafted the manuscript. NA and LM reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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