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Efficacy of Granisetron versus Sufentanil on Reducing Myoclonic Movements Following Etomidate

A double-blind, randomized clinical trial

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Abstract

Objective: Etomidate-induced myoclonus occurs in up to 85% of patients under general anesthesia. This type of myoclonus can induce significant clinical and economic problems in patients with special conditions. Hence, to reduce the intensity of myoclonus movements, the present study was conducted to compare the effectiveness of granisetron and sufentanil on reducing the intensity of etomidate-induced myoclonic movements. ***Methods:*** This double-blind randomized clinical trial study consisted of 96 adult patients. Using block randomization, subjects were divided into three groups of 32: 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 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.

Advances in Knowledge:

- **Clinical Function:** Considering the effectiveness of granisetron in controlling and reducing myoclonic movements during general anesthesia, it can be effective in improving the quality of anesthesia when using in the hospital.
- **Education:** The results of this research can provide a new insight into the use of granisetron in controlling and reducing myoclonic movements during general anesthesia for professors, students, and educational planners.
- **Research:** The results of this research can set the ground for further quantitative studies on the drug granisetron and comparing its effectiveness with other drugs in controlling and reducing myoclonic movements during general anesthesia.

Application to Patient Care:

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

Introduction

Etomidate is an intravenous general anesthetic agent, whose clinical effects are developed through enhancing the GABA inhibitory system by altering chloride conduction.[1] Due to its rapid induction of anesthesia with minimal changes in cardiovascular function, it is one of the most widely used intravenous anesthetics 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 minimized 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 anesthesia.[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 hyperexcitability of a group of neurons in certain cerebral structures, the relationship of myoclonic jerks with EEG activity is of primary importance in the study of myoclonus.[7,8]

Different drugs (fentanyl,[9] remifentanil,[10] midazolam,[11] 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.[12] Fentanyl is a single synthetic opiate used for analgesia. Today, fentanyl is widely used for anesthesia and pain relief. Among the side effects of this drug are itching and impaired breathing.[5,9] As an opioid analgesic, sufentanil is an analog of fentanyl and is used to induce as well as maintain anesthesia plus postoperative analgesia. In practice, it seems that the hemodynamic stability of sufentanil anesthesia 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] In another study in 2016, the incidence of etomidate-induced myoclonus with sufentanil pretreatment was reported to be 28%. [16]

Granisetron is one of the serotonin receptor antagonists that is used as an anti-nausea and vomiting drug in the operation room, chemotherapy, etc.,[17] This drug has minor side effects and may cause headaches, confusion in people who are allergic to the drug, and constipation.[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 study by Alipour M (2013). 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 intensity of myoclonus induced by intravenous administration of etomidate and to compare with sufentanil.

Materials and Methods

This double-blind clinical trial study was performed on selected patients referring to educational hospitals affiliated with Mashhad University of Medical Sciences in 2021. After obtaining the 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), sampling and data collection began. In this study, 96 patients were selected via convenience sampling and randomly based on a table of random numbers created by a computer. Then, 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 anesthesia with (1) American Society of Anesthesiologists Classification (ASA) I, II, (2) and age between 15-60 years. Exclusion criteria included (1) adrenal dysfunction, (2) history of allergy to opioid analgesics and hypnotics drugs, (3) mental disorders, (4) neuromuscular diseases, (5) seizure, (6) electrolyte imbalanced, (7) history of addiction, (8) long QT syndrome, as well as severe cardiovascular diseases, (9) high Intracranial pressure (ICP) and Intraocular pressure(IOP), and (10) increased intra-abdominal pressure. Written consent was obtained from all subjects, and they were assured that all their information would remain confidential. Also, at any time, and even after giving consent, they could withdraw from the study voluntarily (Figure1).

Patients underwent isotonic IV 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 randomization) 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 was evaluated by a person who was not aware of the group allocations (anesthesia resident) 2 minutes after administration of etomidate. The drugs were injected by an anesthetist who was unaware of the type of drugs.

In this double-blind study, the intensity of myoclonus was measured with a score between 0 and 3, where 0 represents no myoclonus, 1 indicates mild as small movements of a part of the

body such as finger or wrist, 2 denotes moderate as gentle movements of two different muscle groups such as face and legs, and 3 indicates severe as 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 the myoclonus, the patient was prescribed a full dose of a narcotic drug (fentanyl 1 microgram/kg), 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 qualitative trait in two communities and taking into account the findings of the study of Alipour et al,[16] who reported the incidence of grade 0 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%.

In this study, descriptive statistical tests, and chi-square as a non-parametric test for qualitative demographic variables and incidence of myoclonus was used. Also, analysis of variance (ANOVA) was performed to compare the mean of quantitative variables between groups using SPSS19 software.

Results

In this study, 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, anesthesia class (ASA), underlying diseases

(hypothyroidism and hyperthyroidism, hypertension, diabetes, and ischemia) based on the chi-square test. Also, 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' hemodynamic 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 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 chi-square 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 (Tables 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 as pretreatment agents to reduce myoclonus induced by etomidate injection has been investigated, such as dexmedetomidine,[20] opioids,[21] benzodiazepines,[21] lidocaine,[22] magnesium sulfate,[20] muscle relaxants, [23,24] gabapentin.[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 that had not been studied before. The efficacy of granisetron was investigated as a pretreatment in a study by Alipour M (2013), 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 0 (without myoclonus)[18]. Since 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 Y et al. (2011) demonstrated that pretreatment with 100 micrograms of fentanyl reduced the incidence of myoclonus by up to 8%. [28] Also, in a study by Stockham RJ et al., higher doses of fentanyl (500 μg) significantly reduced myoclonic movements. However, the incidence of apnea increased during induction.[29]A study by Kelsaka E et al. (2006) demonstrated that remifentanil injection (1μg/kg) 2 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 the study by Alipour et al. (2016), 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 (2022) clarified that etomidate increased the mean behavioral scores and glutamate levels in the CSF plus neocortex during anesthesia. More importantly, they demonstrated a strong correlation between the myoclonus and neocortical glutamate accumulation. In this study, they concluded etomidate-induced myoclonus is associated with neocortical glutamate accumulation. Suppression of the astrogliosis in neocortex and promoting extracellular glutamate uptake by regulating glutamate transporters (EAATs) 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 timing

of pretreatment agents along with the different conditions of patients. The findings of the present study regarding reduction if the intensity of myoclonic movements due to the pretreatment 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 damages or not has not been proven and is debatable.

One of the most important limitations in 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, LM conceptualised and designed the research. PZ, MA and LM were responsible for sampling and intervention. NA was responsible for statistical analysis. PZ, 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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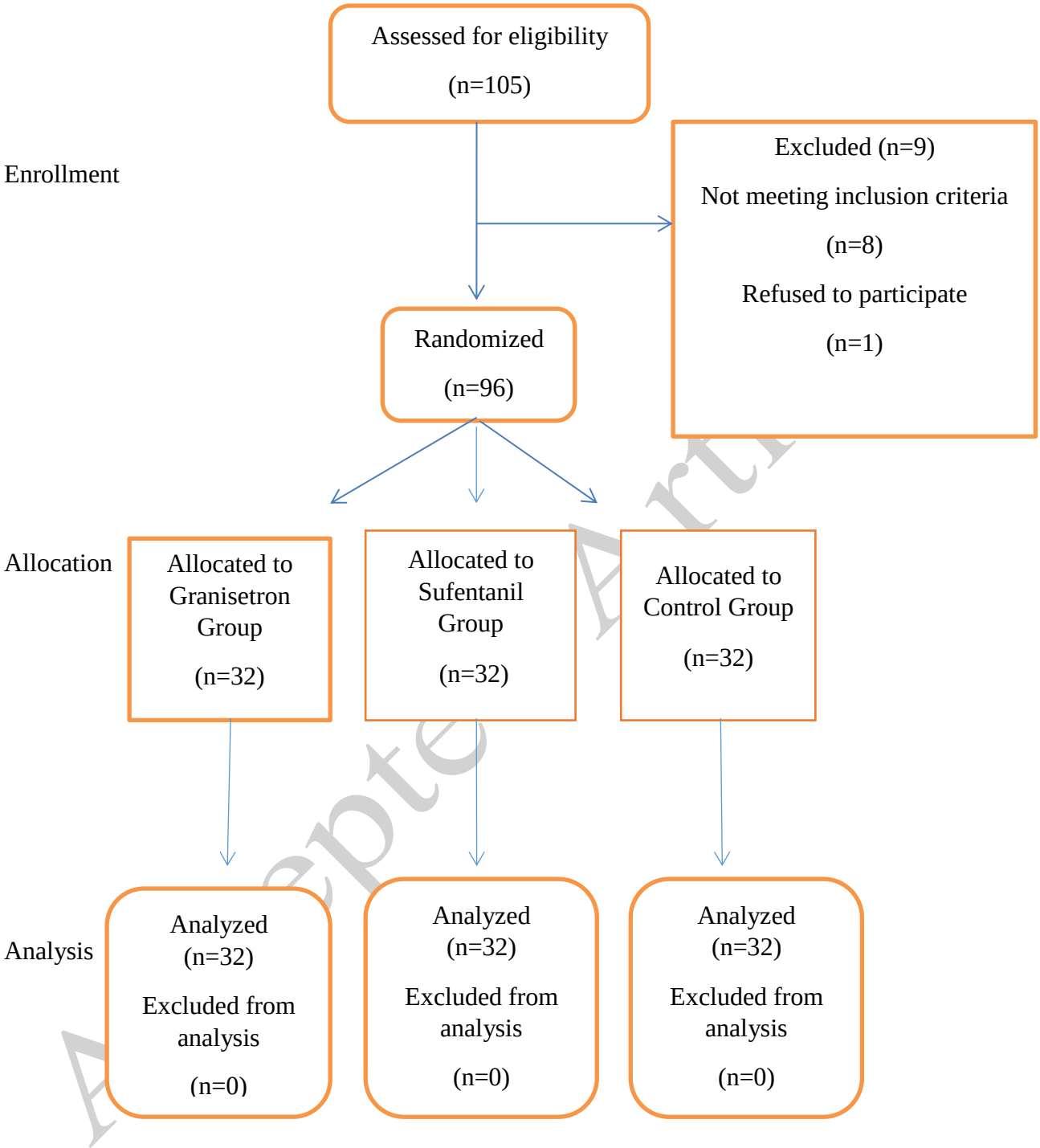

Figure1: The consort flow diagram

Table1. Underlying diseases and demographic variables in the experimental and control groups

Variables		Group						value	*P* value
		Granisetron		Sufentanil		Control			
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	ASAI	21	65/50	26	81/3	22	68/8	2.16	0.33
	ASAII	11	34/50	6	18/2	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	00	0	00	2.02	0.36
	No	31	96.9	32	100	32	100		
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(cm)	-----	172.50	4.62	171.62	5.67	172.69	5.16	5.87	0.82
Weight(kg)	------	73.68	3.84	72.50	4.13	72.40	3.89	6.45	0.89
BMI	------	24.49	1.51	24.41	2.46	24.52	2.25	0.89	0.92

Height, weight and BMI expressed as mean ± Standard deviation. Other variables expressed as frequency and percent.

Table 2: Comparison of hemodynamic variables of patients in three groups 60 seconds before and after injection of studied drugs.

variables	Group						value	P value
	Granisetron		Sufentanil		Control			
	Mean	SD	Mean	SD	Mean	SD	0.81	0.44
Systolic I	135.00	20.85	133.84	23.18	128.25	23.86		
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	88.4	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
SPO2I	99.84	0.51	99.53	0.80	99.72	0.52	0.79	0.14
SPO2II	99.91	0.29	99.98	0.12	99.94	0.25	0.94	0.20

In the table above, hemodynamic variables recorded and measured 60 seconds before injection are marked with Roman numeral I, and variables recorded 60 seconds after injection of the studied drugs are marked with Roman numeral II.

Table 3: The intencity and incidence of myoclonus in the experimental and control groups after injection of etomidate.

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