

# Comparison of the Effects of Low-Dose Midazolam, Magnesium Sulfate, Remifentanyl and Low-Dose Etomidate on Prevention of Etomidate-Induced Myoclonus in Orthopedic Surgeries

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Received 2015 December 07; Revised 2015 December 25; Accepted 2016 January 09.

## Abstract

**Background:** Etomidate is a potent hypnotic agent with several desirable advantages such as providing a stable cardiovascular profile with minimal respiratory adverse effects and better hemodynamic stability compared with other induction agents. This drug is associated, however, with myoclonic movements which is characterized by a sudden, brief muscle contractions as a disturbing side-effect.

**Objectives:** The present study was designed to compare the effectiveness of low-dose midazolam, magnesium sulfate, remifentanyl and low-dose etomidate to suppress etomidate-induced myoclonus in orthopedic surgery.

**Patients and Methods:** A double-blind clinical trial study was conducted in an academic hospital from September 2014 to August 2015. Two hundred and eighty-four eligible patients, American society of anesthesiologists class I - II, scheduled for elective orthopedic surgery were randomly allocated into four equal groups (n = 71). They received premedication with intravenous low-dose midazolam 0.015 mg/kg, magnesium sulfate 30 mg/kg, remifentanyl 1 µg/kg and low-dose etomidate 0.03 mg/kg two minutes before induction of anesthesia with 0.3 mg/kg intravenous etomidate. Then the incidence and intensity of myoclonus were evaluated on a scale of 0 - 3; 0 = no myoclonus; 1 = mild (movement at wrist); 2 = moderate (movement at arm only, elbow or shoulder); and 3 = severe, generalized response or movement in more than one extremity, within ninety seconds. Any adverse effect due to these premedication agents was recorded.

**Results:** The incidence and intensity of myoclonus were significantly lower in the low-dose etomidate group. The incidence rates of myoclonus were 51 (71.85%), 61 (85.9%), 30 (42.3%) and 41 (57.7%), and the percentages of patients who experienced grade III of myoclonus were 30 (58.8%), 32 (52.5%), 9 (30%) and 14 (34.1%) in the midazolam, magnesium sulfate, etomidate and remifentanyl groups, respectively. The incidence and intensity of myoclonus were significantly lower in the low-dose etomidate group (P = 0.0001). No notable adverse effect was detected in our patients during the study period.

**Conclusions:** Intravenous etomidate 0.03 mg/kg prior to induction can effectively reduce the incidence and severity of myoclonus linked to etomidate.

**Keywords:** Midazolam, Magnesium Sulfate, Remifentanyl, Etomidate, Prevention, Myoclonus

## 1. Background

Etomidate as a hypnotic agent was introduced into clinical practice in 1972. It is still widely used due to its several advantageous, extremely stable hemodynamic profile, minimal histamine release, cerebral protection, and pharmacokinetics enabling rapid recovery after either a single dose or a continuous infusion (1-8).

However, it is associated with some disturbing side effects, such as pain on injection, postoperative nausea and vomiting, adrenal suppression, superficial thrombophlebitis and myoclonus (3, 4, 9, 10).

Studies have reported the incidence of myoclonus as high as 50% - 80% in nonpremeditated patients (9, 11). My-

oclonus is defined as sudden, brief, involuntary muscle jerks either irregular or rhythmic. These movements are caused by muscular contractions (12, 13).

The consequences of this adverse effect can be serious in some groups of patients including nonfasted emergency patients with the risk of regurgitation and aspiration, open globe injuries with the raised risk of prolapse of vitreous material and as these muscle contractions increase myocardial oxygen consumption, it is harmful in cases of limited cardiovascular reserve. In addition, during the jerky movements ECG leads may become detached. It should be noted that ECG leads detachment during myoclonic movements leads to delay of monitoring and suc-

cess of early intervention (1, 2, 4, 9, 14).

A number of drugs have been investigated to reduce the rate and intensity of this adverse effect. However, considering that etomidate is a preferred agent in compromised hemodynamically cases and the necessity of prevention of myoclonus in these patients, it seems that this topic still remains attractive and calls for more researches. We expect that findings of this research will be helpful during induction with etomidate in unstable hemodynamic profile patients whom etomidate is the preferred drug on the other hand they have also serious situation such as open globe injury, nonfasting condition or poor cardiac reserve that myoclonus prevention is vital for them.

## 2. Objectives

The current study aimed to compare the effects of low-dose midazolam, magnesium sulfate, remifentanyl and low-dose etomidate as premedication on suppression or reduction of myoclonus induced by etomidate during induction of anesthesia.

## 3. Patients and Methods

This randomized double-blind clinical trial was conducted in an academic hospital in the north of Iran affiliated to Guilan University of Medical Sciences (GUMS) from September 2014 to August 2015. Before sampling, its proposal was approved by the ethics committee of GUMS by reference number of 1930175710 and registered in Iranian registry of clinical trials (IRCT) by number of IRCT2014070613456N1.

### 3.1. Inclusion Criteria

Patients aged between 19 - 59 years, body mass index (BMI) in a normal range, American society of anesthesiologists (ASA) physical status I or II, with one affected limb were scheduled for elective orthopedic surgery under general anesthesia.

### 3.2. Exclusion Criteria

Neuropsychological disease, adrenal cortex dysfunction, heart failure, renal, pulmonary, hepatic or endocrinal diseases, history of allergic reaction to the study drugs (midazolam, magnesium sulfate, remifentanyl, etomidate), those who had received analgesics, sedatives within the previous 24 hours, hiatal hernia and symptomatic gastroesophageal reflux, and pregnant or lactating women.

Patients were randomly allocated into four groups receiving intravenous low-dose midazolam 0.015 mg/kg,

magnesium sulfate 30 mg/kg, remifentanyl 1  $\mu$ g/kg and low-dose etomidate 0.3 mg/kg as premedication.

On arrival in the operating room, firstly fasting status was checked and then an intravenous catheter was inserted into the forearm vein. Standard monitoring, including electrocardiography with both leads II and V5 with automated ST-segment analysis to detect ischemia, pulse oximetry and noninvasive blood pressure (NIBP) with an interval of 3 minutes was applied for all patients.

An anesthesiologist, who was blinded to the study groups, prepared the drugs in 5 mL volumes inside coded injectors. Isotonic saline 5cc/kg was infused over a period of 10 minutes. When the infusion was completed, preoxygenation was achieved by O<sub>2</sub> 100% via a face mask then in each group the mentioned drug was administered as pre-treatment. After two minutes intravenous etomidate 0.3 mg/kg was injected, over sixty seconds. As the incidence of myoclonus induced by etomidate depends on the dosage and speed of injection, it was administered in the same injection rate and dosage to all our cases (15).

A physician who was blinded to the group allocation observed myoclonic movements within ninety seconds after etomidate injection was finished. It is known that in more than half of the cases myoclonus induced by etomidate begins after sixty seconds; therefore, our cases were observed for 90 seconds. The intensity and frequency of myoclonus were evaluated using a scale of 0 to 3; 0 = no myoclonus; 1 = mild (movement at wrist); 2 = moderate (movement at arm only, elbow or shoulder); and 3 = severe, generalized response or movement in more than one extremity (15-17).

After evaluation of myoclonus all patients received fentanyl 3  $\mu$ g/kg (except for remifentanyl group). When neuromuscular blockade was achieved with cisatracurium 0.15 mg/kg, trachea was intubated and maintenance of anesthesia was provided by continuous infusion of propofol 50 - 150 mg/kg/min, sufentanyl 0.1 - 0.3  $\mu$ g/kg/h and cisatracurium 0.6 mg/kg/h.

### 3.3. Statistical Analysis

The data were registered and analyzed using the SPSS software version 19.0 for windows software to compare the categorical data among the groups. Data were shown as mean  $\pm$  SD. Demographic data of the patients in four groups (age, weight, and height) were analyzed using one-way ANOVA, whereas gender was analyzed using the chi-square test. Intensity of myoclonic movements in four groups were presented as ranked data (mild, moderate, severe) and compared by the Mann-Whitney-Wilcoxon test. A P value < 0.05 was considered to be significant.

#### 4. Results

Two hundred and eighty-four cases who met the inclusion criteria enrolled the trial, during the study period. They were randomly assigned to four treatment groups and completed the survey. In terms of demographic data (age, gender, BMI and ASA physical status) there was no significant difference among the groups (Table 1). The incidence rates of myoclonus were 51 (71.85%), 61 (85.9%), 30 (42.3%) and 41 (57.7%) in the midazolam, magnesium sulfate, etomidate and remifentanyl groups, respectively ( $P = 0.0001$ ). The percentage of patients who experienced severe form (grade III) of myoclonus was significantly lower in the low-dose etomidate group ( $P = 0.0001$ ) (Table 2).

None of the patients in four groups was affected by any side effect related to the mentioned drugs used as premedication.

#### 5. Discussion

Etomidate as a water and fat soluble carboxylate imidazole is a popular hypnotic agent. It is frequently used for hemodynamically unstable patients (3, 4, 7). In spite of its several benefits, myoclonus as nonepileptic involuntary jerky movements of muscles still remains as a notable side effect (18). The true mechanism of etomidate-induced myoclonus is not clear; however, one postulated mechanism for etomidate-induced myoclonus is that larger concentrations of etomidate depress cortical activity earlier than subcortical activity. For this reason, myoclonus can be prevented by premedication with known agents to inhibit subcortical neuronal activity.

Regional receptor distribution differences and inhomogeneous local blood flow within the central nervous system (CNS) causes the unsynchronized onset of drug action at different sites of CNS. In fact, a temporary disequilibrium of the effect is produced and leads to an earlier depression of cortical inhibition. Etomidate acts at the GABA<sub>A</sub> receptor. Pathways that control skeletal muscles and spontaneous neuronal discharge are sensitized by cutting GABA neuronal transmission and cause myoclonic contraction. High doses of etomidate interacts with GABA<sub>A</sub> receptors of central nervous reticular activating system and directly activate the receptors, however lower doses have a modulating effect. The ability to modulate and activate GABA<sub>A</sub> receptors depends on the  $\beta$ -subunit type of the receptor. Therefore, the different distribution of GABA<sub>A</sub> receptor subunits within the CNS explains the reason of a regionally distinct effect of the drug. It is indicated that inhibitory circuits are depressed sooner and at lower doses of etomidate than excitatory circuits. Therefore, it

is thought that pretreatment with etomidate could diminish myoclonus related to the drug. Conversely, large bolus doses of etomidate leads to the increases of myoclonus (6, 9, 11, 19-22).

Considering that etomidate is an attractive induction agent in unstable hemodynamic patients and the risks created by myoclonus for the patient, a preventive approach is preferable and it is important to blunt these unacceptable movements.

A variety of drugs are known that reduce myoclonus due to etomidate to different extents such as dexmedetomidine (1), opioids (4, 6, 18, 22-24) benzodiazepines (25-27), lidocaine (5, 28), magnesium sulfate (5, 21, 29), muscle relaxants (17, 30), gabapentin (14) thiopental (31) and dezocine (32). However, offending drugs should be strictly limited to accurate indications. It is important to choose an optimal agent as premedication regarding to the type and duration of the surgery and patient's condition.

So, we conducted a double-blind trial to compare the effects of low-dose midazolam, magnesium sulfate, remifentanyl and low-dose etomidate for prevention or reduction of myoclonus due to etomidate. Studies have indicated the efficacy of these agents for this purpose. However, among similar studies there has been no study comparing these four agents. It might be the special feature of the present research but leads to some limitations in comparing the result with the other studies. We found that among these four drugs, low dose of etomidate was the most effective one to control myoclonus due to etomidate. The percent of our patients who presented myoclonus and also who developed grade III were significantly lower in the low-dose etomidate group. The number of patients who experienced grade I was significantly more than the other three groups. However, the difference was not significant for grade II. Carlos and Innerarity (33) reported that premedication by fentanyl plus atropine or with diazepam plus atropine reduced the frequency of myoclonic movements after induction of anesthesia with etomidate. Their case selection was among adult patients undergoing elective orthopedic surgery.

Yilmaz Cakirgoz et al. (14) reported that pretreatment with 800 mg gabapentin orally 2 hours before surgery reduced the incidence and severity of myoclonus due to etomidate. It is noticeable that in the period before surgery, 60% - 80% of patients experience stress and anxiety about anesthesia and surgery, which results in delay in gastric emptying (34, 35).

Therefore, it is thought that orally administration of medications and their peak plasma concentration levels are affected by preoperative stress. As the degree of stress and anxiety are different among individuals, it seems that our results might be more reliable than the similar stud-

**Table 1.** Baseline Characteristics of Patients in Four Groups

	Etomidate	Remifentanil	Mg Sulfate	Midazolam	P Value
Age, y	35.21 ± 11.58	38.95 ± 12.25	36.78 ± 11.56	36.73 ± 11.68	0.304
BMI, kg/m <sup>2</sup>	26.26 ± 3.31	25.64 ± 2.63	26.31 ± 2.43	25.73 ± 3.62	0.428
Gender					0.22
Female	13	23	16	20	
Male	58	48	55	51	
ASA					0.917
I	62	60	63	61	
II	9	11	8	10	

**Table 2.** Severity and Incidence of Myoclonic Movement After Etomidate Injection in Four Groups

Group/myoclonus	Etomidate	Remifentanil	Mg Sulfate	Midazolam	Total	P Value
Grade						0.0001
I	12 (40)	12 (29.3)	4 (6.6)	3 (5.9)	31 (16.9)	< 0.0001
II	9 (30)	15 (36.6)	25 (41)	18 (35.3)	67 (36.6)	0.739
III	9 (30)	14 (34.1)	32 (52.5)	30 (58.8)	85 (46.5)	0.018

ies, which had orally administered drugs as pretreatment (14).

Opioids effectively reduce these movement, but at the cost of undesirable side effects such as respiratory depression, apnea nausea and vomiting (9, 20). One of our pretreatment agents was remifentanil, which is a selective  $\mu$  receptor agonist. It is metabolized rapidly with a short acting duration (23). Kelsaka et al. (22) stated that remifentanil as a short acting opioid is effective in prevention of myoclonus but can cause severe bradycardia and chest rigidity. We chose the remifentanil dosage following the previous studies with promising results in which remifentanil 1  $\mu$ g/kg as pretreatment was effective with no side effects and with a stable statue of hemodynamics (6, 23).

Ko et al. (6) reported that by administration of remifentanil 1  $\mu$ g/kg the incidence of myoclonus reduced to 3.3% and severe myoclonus was not observed in any of the cases. The dosage of remifentanil was similar to the dosage used in our study, but it takes into consideration that the mean age of the studied patients was 68.9 ± 4.6 and the mean of weight was 59.0 ± 10.5 in their research compared to 36.91 ± 11.69 and 72.21 ± 8.85, respectively in our study. Also, they used smaller dosage of etomidate for induction of anesthesia.

Lee et al. (16) reported that pretreatment with remifentanil 1  $\mu$ g/kg significantly reduced the incidence of etomidate-induced myoclonus in patients scheduled for elective plastic surgery; 16.7% of their patients developed

myoclonus and none of them were in grad III. Comparing these findings to our study, the superiority of their results might be partly explained by the difference between selected patients population regarding to the gender, female/male ratio was higher in their study (87% vs 47%). As it is indicated the occurrence of myoclonus is affected by some factors such as sex, age and the dosage of etomidate (16, 36).

Hwang et al. (37) compared the effects of midazolam 0.5 mg/kg with remifentanil 1  $\mu$ g/kg on myoclonic movement following etomidate injection; in contrast to our findings that indicated the superiority of remifentanil to midazolam, they reported that there was no significant difference in the incidence of myoclonus between the two groups. The difference might be explained by a larger dosage of midazolam (0.5 mg vs 0.15 mg).

The other agent we used as premedication was midazolam, a short acting benzodiazepine, which acts selectively through the GABA<sub>A</sub> receptor. This receptor mediates fast inhibitory synaptic transmission (38). Korttila et al. (39) investigated the effects of diazepam on etomidate-induced myoclonus, but the results were disappointing and diazepam failed to reduce myoclonus. However, studies have indicated the positive effects of midazolam on prevention of myoclonus. The reason might be the faster onset of midazolam (38).

Huter et al. (27) demonstrated that intravenous midazolam 0.015 mg/kg administered 90 seconds before in-

duction of anesthesia with etomidate is effective in reducing myoclonic movements. Myoclonus developed in 10% of their cases, the drugs dosage were the same as used in our study; however, the superiority of their result (10% vs 71.85%), might be partly due to the difference between the patients in two groups, regarding to ASA class (III, IV vs I, II) and sample size (20 vs 71).

Wasinwong et al. (26) found that midazolam 0.03 mg/kg before 0.15 mg/kg etomidate resulted in myoclonus in 60% of patients. Our results showed 71.8% myoclonus in the midazolam group. Comparing the reported results, the difference might be explained by the larger dosage of midazolam and the dosage of etomidate, which was in the subhypnotic range. Salim et al. (20) gave midazolam 0.05 mg/kg 90 seconds before etomidate 0.3 mg/kg injection. Myoclonus developed in 15.45% of patients and the severe form was observed in 1.6% of cases. Although these results seem better than ours; however, they had some noticeable limitations such as, their study was a case series and patient selection was not randomized and female gender was significantly dominant among the patients. The other premedication was magnesium sulfate, an antagonist of N-methyl-D aspartate (NMDA) receptor. When this receptor is activated calcium influx into the cell occurs and then nitric oxide production would be increased (29).

Un et al. (21) demonstrated that by administration of 60 mg magnesium sulfate 3 minutes before the etomidate injection 0.3 mg/kg, myoclonus movements were observed in 26% of their patients, however it was up to 85% of our cases in the magnesium sulfate group. Although we used larger dosage of magnesium sulfate and similar dosage of etomidate, the difference between the results might be explained by the rate of injection of etomidate, the time of the evaluation and patients' BMI, which are impact factors that were not found in their method section.

In addition, the intensity of movement based on 0 - 3 scale grading was not evaluated. Also, ASA class II was more dominant in their study, which affects the results. It is known that hypnosis agents can also blunt myoclonus movements. Based on the Doenicke et al. study the etomidate dosage was 0.03 mg/kg in our study (11).

We cannot ensure that low doses of etomidate are a superior agent to other drugs, but it is advantageous that the mentioned adverse effects related to the other three agents do not occur.

Generally, different results might be multifactorial and partly stem from the dosage and the route and timing of administration of premedication agents and the patients' different structures regarding to population selection.

### 5.1. Suggestions

Noticing the importance of the issue, further studies are required to determine the minimal dosage of the drugs that can suppress these movements without generating side effects.

Efficacy and tolerability of the short acting pretreatment agents should be confirmed to find the optimal dosage with minimal effects on respiratory and hemodynamics. The recovery time from anesthesia should be regarded as well.

### 5.2. Limitations

The primary limitation is that our patients were younger and healthier than the patient group to whom etomidate is most frequently administered. Therefore, generalizations of our findings should not be made for high risk or geriatric population who might have comorbidities and be more sensitive to these types of drugs. The second limitation is, even though we compared the effectiveness and safety of these drugs as premedication, there was no "control group". If we had one, our results could be more supportive for this opinion and could make this study be more strengthened.

### 5.3. Conclusions

This study showed that pretreatment with low-dose etomidate before etomidate induction can significantly reduce the incidence and severity of myoclonus. This agent is recommended as premedication because it is associated with fewer side effects.

### Acknowledgments

The authors wish sincerely to thank the support of all the colleagues in Poorsina hospital medical center affiliated to Guilan University of Medical Sciences in Rasht, Iran.

### Footnotes

**Authors' Contribution:** Abbas Sedighinejad: study design and conduct, data analysis, and manuscript preparation; Bahram Naderi Nabi: study design, data collection, manuscript preparation and data analysis; Mohammad Haghghi: study design, data analysis, and manuscript preparation; Gelareh Biazar: study design, data collection, manuscript preparation, and data analysis; Vali Imantab: data analysis and manuscript preparation; Siamak Rimaz: manuscript preparation and data analysis; Zahra Zaridoost: manuscript preparation.

**Funding/Support:** This study was financially supported by anesthesiology research center, Guilan University of Medical Sciences (GUMS), Rasht, Iran.

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