

Short Communication**Prevention of etomidate-related myoclonus in anesthetic induction by pretreatment with magnesium***Bulent Un¹, Dilek Ceyhan², Birgul Yelken³***Abstract**

BACKGROUND: Etomidate frequently leads to myoclonic jerks during anesthetic induction. This study aimed to detect if pretreatment with magnesium decreases myoclonus incidence.

METHODS: A hundred ASA (the American Society of Anesthesiologists) I-II patients were included and randomized into 2 groups. Three minutes before etomidate induction of anesthesia (by 0.3 mg/kg intravenous etomidate), Group M received 2.48 mmol (60 mg) intravenous magnesium sulphate and Group P received equal volume of intravenous saline. Myoclonus was evaluated as "present/absent".

RESULTS: The rate of myoclonus was significantly lower in Group M than in Group P ($p < 0.01$). Hemodynamic parameters revealed no significant difference between the two groups.

CONCLUSIONS: Low dose magnesium pretreatment before etomidate induction of anesthesia significantly reduces unwanted myoclonic jerks and also protects the hemodynamic stability.

KEYWORDS: Etomidate, Myoclonus, Magnesium Sulphate.

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Etomidate is a carboxylated imidazole derivative widely used as an intravenous anesthetic induction agent. Its cardiovascular side effects are very small and therefore it is especially preferred in patients with unstable hemodynamic status. However, it has some side effects like injection pain, postoperative nausea/vomiting, electroencephalography (EEG) activation, adrenal suppression and myoclonus. The incidence of myoclonus has been reported as much as 50-80% after etomidate induction.¹

Although the mechanism of the myoclonus is not clear, various drugs, such as opiates, benzodiazepines, and rocuronium are given before etomidate induction in order to prevent myoclonus.²⁻⁴ Small doses of ketamine and magnesium are shown to decrease injection pain of propofol. They are also thought to be

effective against injection pain of etomidate and myoclonus.^{5,6}

This study was conducted to detect if magnesium can decrease myoclonus incidence after etomidate induction.

Methods

This prospective, randomized, placebo-controlled study was performed in Osmangazi University Hospital, Eskişehir, Turkey. It was approved by the hospital's Ethics Committee (2008/35). Randomization was performed using sealed envelope method. Informed written consents were taken from 100 ASA (American Society of Anesthesia) I-II patients who were scheduled to undergo elective transurethral resection of prostate surgery and bladder cancer cystoscopy. Patients with serious heart failure, renal, pulmonary, hepatic and

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endocrinal diseases were excluded. Re-operated patients and those having coagulopathies or drug allergies were also excluded. No premedication was given before surgery.

In the operation room, patients were monitored on the table for standard electrocardiography, heart rate, non-invasive blood pressure and pulse-oximetry. A 20-gauge intravenous catheter was placed on dorsum of hand. An anesthetist blinded to the study procedure prepared the drugs in 5 ml volumes inside coded injectors. Patients were randomized into two groups. The first group (M) received 2.48 mmol (60 mg) magnesium sulphate as intravenous bolus injection. Three minutes after magnesium, 0.3 mg/kg intravenous etomidate was administered as general anesthetic induction. The second group (P) received saline. In order to facilitate endotracheal intubation, 0.5 mg/kg intravenous atracurium was given one minute after etomidate. After intubation, maintenance was provided by 50/50 N₂O/O₂ and 2% sevoflurane (via inhalation).⁷ The presence of myoclonus was checked and recorded as "present/absent". Systolic, diastolic and mean arterial pressures, heart rates, and peripheral oxygen saturations were recorded during pre-induction and post-induction periods, and also after intubation at 1st, 2nd, 5th, 10th and 20th minutes.

The incidence of myoclonus in the control group was expected to be 80% based on previous studies.⁴ A minimum of 30 patients in each group was required to detect a 50% difference in the incidence of myoclonus at a significance level of 95% and a power of 90%. We decided to include 50 patients in each group. SPSS 13 (Statistical Package for the Social Sciences, SPSS, Inc., Chicago, IL) was used for statistical analysis. T-test was used for comparison of measured variables in the two groups with normal distribution. Two-way repeated analysis of variance (ANOVA) was used to detect the significance of variables at different time intervals. Mann Whitney U test was used to detect the difference between measurements. Pearson's chi-square test was used for

cross-analysis of categorical data. Normality tests were conducted by Kolmogorov-Smirnov and Shapiro-Wilk tests. The results are shown as mean \pm standard deviation (SD). A $p < 0.05$ was considered as significant.

Results

Table 1 shows the demographic data in which the two groups were not significantly different ($p > 0.05$). The evaluation of myoclonus in the two groups is shown in Table 2. The presence of myoclonus in Group M was found to be significantly lower than Group P ($p < 0.01$) (Table 2).

There were no significant differences between the two groups were observed in terms of systolic, diastolic and mean arterial pressures (Figure 1), heart rates (Figure 2), peripheral oxygen saturations during pre-induction and post-induction periods, or at 1st, 2nd, 5th, 10th and 20th minutes after intubation ($p > 0.05$).

Table 1. Demographic features of the patients.

	Group M (Magnesium)	Group P (Placebo)
Patient number	50	50
ASA (I/II)	28/22	27/23
Age (year)	34.5 \pm 9.3	32.5 \pm 9.9
Sex (female/male)	23/27	22/28
Weight (kg)	74.5 \pm 8.1	71.9 \pm 9.3

Data are presented as numbers or mean \pm SD.

Table 2. Distribution of myoclonus in the two groups.

Myoclonus	Absent	Present
Group M (Magnesium)	37 (74%)	13 (26%)
Group P (Placebo)	22 (44%)	28 (56%)
Total	59	41

Discussion

Based on the results of this study, pretreatment with intravenous magnesium sulphate at 2.48 mmol (60 mg) dose 3 minutes before general anesthetic induction significantly reduces myoclonic jerks. It also preserves the hemodynamic stability, which is the biggest advantage of etomidate. Moreover, no serious adverse effects were observed.

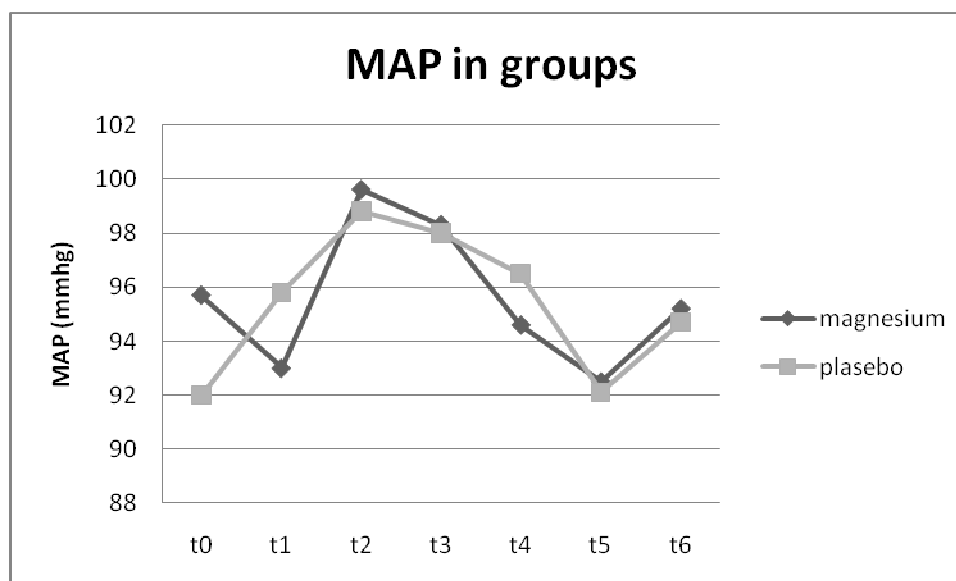


Figure 1. Mean arterial pressures (MAP) in the two groups.

t0: Pre-induction period; t1: Post-induction period; t2: At the 1st minute after intubation; t3: At the 2nd minute after intubation; t4: At the 5th minute after intubation; t5: At the 10th minute after intubation; t6: At the 20th minute after intubation.

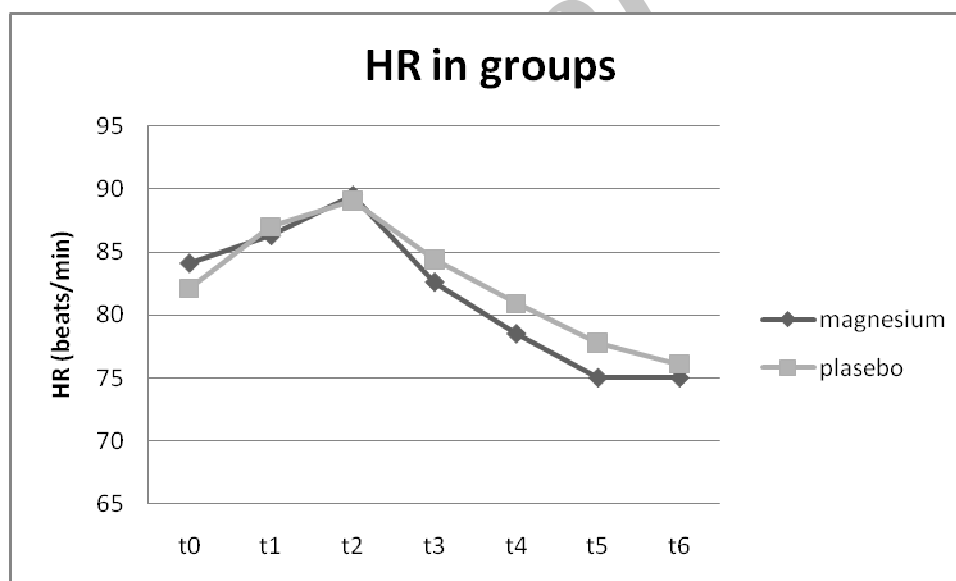


Figure 2. Heart rates (HR) in the two groups.

t0: Pre-induction period; t1: Post-induction period; t2: At the 1st minute after intubation; t3: At the 2nd minute after intubation; t4: At the 5th minute after intubation; t5: At the 10th minute after intubation; t6: At the 20th minute after intubation.

Although many drugs have been investigated for myoclonus, the mechanism of myoclonus due to etomidate is still not apparent enough. Doenicke et al.¹ suggested that myoclonus does not originate from an epileptic focus, instead it arises because of subcortical dis-

inhibition. Subcortical disinhibition also leads to irritable leg syndrome (ILS) during normal sleep. Myoclonus is very similar to ILS which is characterized by uncomfortable legs, irritability, disability to sleep, and numbness. However, the neurological examination is perfectly

normal in this syndrome. In other words, cutting gamma-aminobutyric acid (GABA) neuronal transmission leads to sensitization of pathways that control skeletal muscles and spontaneous neuronal discharge cause myoclonic contractions.⁸ Ates et al. revealed etomidate to have neuroprotective activity in diabetic rats.⁹

Magnesium significantly decreased myoclonus incidence in our study. In a previous study, magnesium prevented myoclonus and magnesium has been suggested to have a different mechanism from other agents preventing myoclonus.⁵ Magnesium is an antagonist of N-methyl-D-aspartate (NMDA) receptors. Activation of this receptor leads to calcium influx into the cell and increased nitric oxide production.⁵ Moreover, nitric oxide is associated with nociception at venous system.⁶ Magnesium also blocks inositol 1, 4, 5-triphosphate (IP₃) mediated calcium channels.^{5,10} Güler et al. compared low dose magnesium and ketamin in preventing the injection pain of etomidate and found ketamin to be superior. However, there were unwanted effects including respiratory depression and sedation in the ketamin group.⁵

Memis et al. successfully used 2.48 mmol (60 mg) magnesium to prevent propofol injection pain.¹¹ Further studies are recommended with different doses of magnesium. In our study, we preferred magnesium a dose at which it is supposed to prevent propofol injection pain.¹¹ It is already known that etomidate injection is painful, especially if it is administered through small veins. We have shown that this specific dose of magnesium significantly reduces myoclonus incidence after etomidate induction. Thus, there might be some correlation between the incidence of injection pain and

myoclonus. Besides, in contrast with opiates, benzodiazepines and ketamine, magnesium does not cause respiratory depression or sedation.

In previous studies, pretreatment with opiates significantly reduced myoclonus.^{12,13} Although Stockham et al. did not find a significant decrease in myoclonus incidence using pretreatment with 100 µg fentanyl before etomidate, they observed significant decrease with higher doses. However, these high doses caused increased incidence of apnea at induction.¹² Canessa et al. showed that fentanyl and alfentanil significantly reduced myoclonus after etomidate in elective cardioversion cases. However, they encountered residual respiratory depression after this procedure.¹⁴ Schwarzkopf et al. observed decreased myoclonic incidence after midazolam (0.015 mg/kg intravenously). Although midazolam protected the hemodynamic stability advantage of etomidate, the disadvantages were respiratory depression and sedation.³

Considering the adverse effects of drugs other than magnesium, prevention of myoclonus alone can be an advantage for magnesium itself. However, further studies are still needed to compare magnesium against midazolam and opioids.

We showed that myoclonus can be prevented using pretreatment with magnesium before etomidate induction. Hemodynamic data revealed no significant difference between groups and etomidate provided excellent hemodynamic stability. During general anesthetic induction, low doses of intravenous magnesium can be preferred to significantly reduce myoclonus side effects of etomidate. In addition, hemodynamic stability is preserved.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

BU carried out the design and coordinated the study. DC participated in most of the study and prepared the manuscript. BY provided assistance in all the study. All authors have read and approved the content of the manuscript.

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