

## Effectiveness of Midazolam in the Prevention of Etomidate Induced Myoclonus

Bushra Salim\*, Safia Zafar Siddiqui, Faisal Shamim and Saeeda Haider

Agha Khan University Hospital Karachi Karachi, Sindh, Pakistan

\*Corresponding author: Bushra Salim, Agha Khan University Hospital Karachi, Anesthesiology, Stadium road Karachi, sindh 74800, Pakistan, Tel: 00923002512868; E-mail: [drbushrasalim@hotmail.com](mailto:drbushrasalim@hotmail.com)

Received date: July 18, 2014, Accepted date: Feb 11, 2015, Published date: Feb 16, 2015

Copyright: © 2015 Salim B, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Introduction:** Etomidate, the imidazole derivative, is an intravenous anaesthetic induction agent, having stable hemodynamic profile, minimal respiratory side effects and histamine release. It is extremely useful in hemodynamically compromised patients. But the most common problem associated with its induction is myoclonus.

**Objective:** To determine the effect of pretreatment with midazolam on the frequency of myoclonus after etomidate induction.

**Methods:** Two hundred and fifty patients fulfilling the inclusion and exclusion criteria, scheduled for elective surgical procedures, were included. After all monitoring and intravenous access, the patients were given intravenous midazolam 0.05 mg/kg and after ninety seconds anesthesia induction was done with etomidate, and the myoclonic movements were noted for a minute after etomidate injection. The movement were recorded and graded on a scale of 0 to 3.

**Results:** Myoclonus was developed in 15.45% (38/246) cases while in 84.55% (208/246) patients abnormal muscle movements was not observed after etomidate injection. Mild myoclonus (grade 1) was observed in 23 (9.3%) cases, moderate myoclonus (grade 2) in 11 (4.5%) and severe (grade 3) in 4 (1.6%) cases.

**Summary:** The incidence of myoclonus was lowered significantly (15.45%) after 0.05mg/kg midazolam pretreatment.

**Keywords:** Etomidate; Myoclonus; Midazolam

### Introduction

Etomidate, an imidazole derivative, is potent hypnotic agent used for intravenous anaesthetic induction. It has stable hemodynamic profile, minimal respiratory side effects and no histamine release. It is very useful in hemodynamically compromised patients [1,2]. The most common problem associated with etomidate at induction of anaesthesia is myoclonus. Myoclonus is involuntary jerky movements, which has clinical significance, as it increases the risk of regurgitation and aspiration. In the case of elective cardioversion where etomidate is quite useful, continuous ECG recordings can be disturbed due to these myoclonic movements [3,4]. Studies show that 50 to 80% of patients who do not receive any pre-treatment after etomidate develop myoclonus [5,6].

A number of drugs have been investigated for suppression of etomidate-induced myoclonus. Ideally, a pre-treatment drug should be short acting with no significant effects on respiration and hemodynamics and should not prolong the recovery from anaesthesia. Opioids can effectively reduce myoclonic movements [7,8], but at the cost of undesirable side effects like respiratory depression and apnea [9].

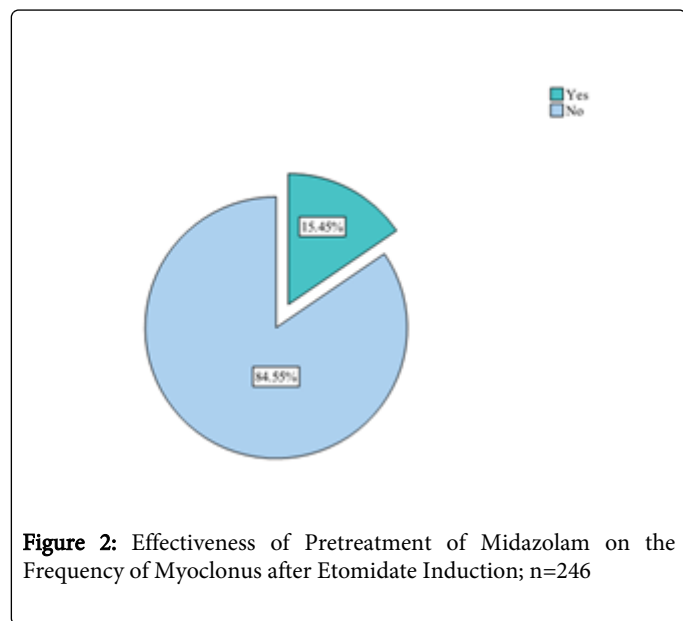
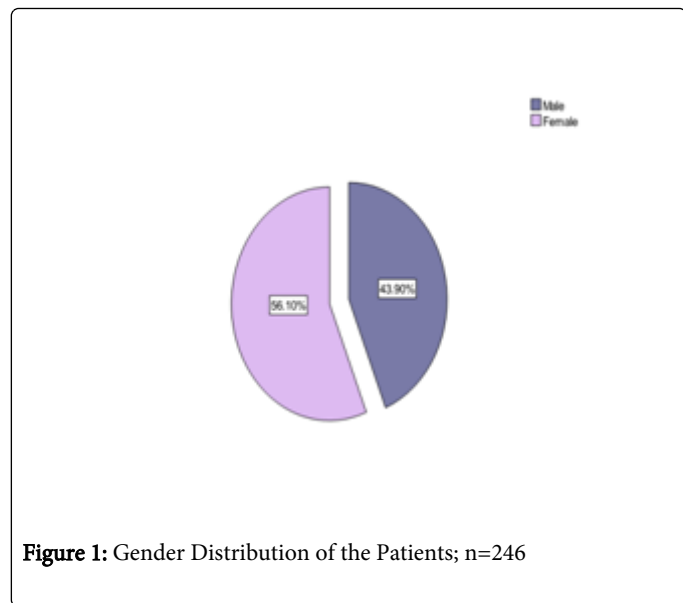
Although benzodiazepines, like midazolam, have been investigated as pre-treatment drugs before the induction of anaesthesia with etomidate to prevent myoclonus internationally, there is no local data

present in this regard. The aim of our study was to determine the effect of pretreatment of midazolam on the frequency of myoclonus after etomidate induction.

### Methodology

After approval from hospital ethics committee, informed consent was taken. A total of 246 patients were selected via the non-probability consecutive technique. The study was conducted at the Department of Anaesthesiology, Surgical Intensive Care and Pain Management, Civil Hospital Karachi, Dow University of Health Sciences, for a period of 6 months. Adult patients between 20 to 50 yrs, either male or female with ASA I & II physiologic score, scheduled for all elective general surgical procedures under general anaesthesia were included. The patients with any neurological disease, those who receive opioid analgesics in the previous 24 hrs and known drug allergies were excluded. No premedication was used.

In the operation theatre, all patients were monitored with ECG, pulse oximeter and non-invasive blood pressure; an 18 G cannula was inserted and intravenous fluid was started. Ninety seconds after administration of midazolam 0.05 mg/kg, induction of anaesthesia was done with etomidate 0.3 mg/kg. One minute after etomidate, atracurium 0.5 mg/kg was given to facilitate intubation. Anaesthesia was maintained with isoflurane 1-1.5% in oxygen and nitrous oxide. All patients were given nalbuphine 0.1 mg/kg for analgesia.



Variables	Mean ± SD	95%CI	Median	Max-Min
			(IQR)	
Age ( years)	36.87±9.81	35.64 to 38.10	40(17)	50-20
Weight (kg)	60.37±10.94	58.99 to 61.75	60(20)	100-30
Height (cm)	159.78±7.50	158.84 to 160	160(11)	184-140

Table 1: Descriptive Statistics of Study Variables; n=246

Myoclonic movements were evaluated clinically which were observed and graded on a scale between 0-3, for a minute after etomidate injection. The grading of myoclonus is: 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 >one extremity

Data was analyzed by using SPSS version 16. Frequency and percentages were computed for categorical variables like gender, ASA status & myoclonus. Mean ± standard deviation was computed for numerical variables age, weight and height.

## Results

All patients included in the trial had completed the study. There was no significant difference among patients with respect to age, weight and height (Table 1). Regarding gender distribution, female patients were more studied than males (Figure 1). According to physical status, 193(78.46%) patients were ASA I while 53(21.54%) were ASA II.

Effectiveness of pretreatment with midazolam on the frequency of myoclonus after etomidate induction is presented in Figure 2. Myoclonus was developed in 15.45% (38/246) cases while in 84.55% (208/246) patients, abnormal muscle movements was not observed, so midazolam was highly effective in the prevention of etomidate induced myoclonus. Severity of myoclonus on a graded scale was also observed (Table 2). Mild myoclonus (grade 1) was observed in 23(9.3%) cases, moderate myoclonus (grade 2) was 11 (4.5%) and severe (grade 3) was 4 (1.6%) cases as presented in table 2. Average age of the patients who developed myoclonus was 36.53 ± 9.51 years and weight and height of the myoclonus patients was 62.95 ± 12.16 kg and 161.87 ± 9.00 cm respectively.

Grading	Frequency	Percentage
0	208	84.60%
1	23	9.30%
2	11	4.50%
3	4	1.60%

Table 2: Grading of Myoclonus; n=246; 0 No Movement; 1 Mild, Movement at wrist; 2 Moderate, Movement at arm only, elbow or shoulder; 3 Severe, generalized response or movement in one extremity

## Discussion

The results of this study demonstrate that pretreatment with midazolam 0.05 mg/kg intravenously significantly reduced the incidence of myoclonic movements during induction of anaesthesia with etomidate.

Despite the variety of drugs potentially reducing the incidence of myoclonic movements after etomidate administration, the mechanism by which this effect is achieved remains unclear. Etomidate interacts with gamma amino butyric acid type A (GABAA) receptors suppressing the central nervous reticular activating system. Doenicke et al. reported a significant reduction of the incidence of myoclonus when diazepam 0.1 mg/kg was given 5 min before etomidate [8].

In 2003, Schwarzkopf and colleagues compared the effect of pretreatment with etomidate of midazolam versus placebo on the incidence and severity of myoclonus following etomidate induction. They concluded that pretreatment with midazolam is effective in reducing the incidence of myoclonic movements while preserving the

advantage of etomidate; that is, cardiovascular stability and short duration of action [3]. Huter et al. investigated the effects of low dose intravenous midazolam pretreatment 0.015 mg/kg on the incidence and severity of myoclonus during induction of anaesthesia with etomidate for elective cardioversion in un-premedicated patients and it was found that 10% of patients in midazolam group had myoclonic movements as compared to 50% receiving placebo [10].

Although opioids have been shown to reduce myoclonus, their mechanism of action still remains unclear. Administration of opioids may be undesirable for short-term procedures because of potential respiratory depression. Stocham et al reported that premedication with fentanyl decreased etomidate-induced myoclonus in a dose-dependent manner, but it increased the risk of apnea [11]. They observed that none of the patients who received premedication with 500 µg fentanyl 5 minutes before anesthesia induction using etomidate had a myoclonus, but all developed apnea. Respiratory depression was less when 100 µg fentanyl was given, and the rate of myoclonus was 33%. Recently, a retrospective comparative study [12], comparing fentanyl, midazolam and fentanyl midazolam combination for prevention of etomidate induced myoclonus showed that incidence of myoclonus was significantly lower in fentanyl (40%) and fentanyl midazolam combination groups (25%) as compared to midazolam alone (70%), that is in contrast to our results.

The rate of injection of etomidate also has an effect on the development of myoclonic movements. Sang Hwan Do et al. conducted a prospective randomized controlled study to compare the effect of the two different etomidate infusion rates on the incidence and severity of myoclonus [13]. They found the slower rate of injection to be effective in reducing the incidence of myoclonus following etomidate induction.

There are some study limitations like study design which is a case series, non random patient selection and predominant female population. We can summarize our study that pretreatment with midazolam (0.05 mg/kg IV) modifies the induction of anaesthesia with etomidate by reducing the frequency of myoclonic movements and therefore, effectiveness of midazolam in the prevention of etomidate induced myoclonus has been shown in our population. We recommend that randomized controlled trials on prevention of etomidate induced myoclonus in our population, are needed.

## References

1. Giese JL, Stanley TH (1983) Etomidate: a new intravenous anesthetic induction agent. *Pharmacotherapy* 3: 251-258.
2. Goodman-Gilman A, Rall TW, Nies AS, Tayler P (eds.) (1990) *The pharmacological basis of therapeutics* (8th edn.) Pergamon Press, New York, pp.305.
3. Schwarzkopf KR, Hueter L, Simon M, Fritz HG (2003) Midazolam pretreatment reduces etomidate-induced myoclonic movements. *Anaesth Intensive Care* 31: 18-20.
4. Hwang JY, Kim JH, Oh AY, Do SH, Jeon YT, et al. (2008) A comparison of midazolam with remifentanyl for the prevention of myoclonic movements following etomidate injection. *J Int Med Res* 36: 17-22.
5. Ruth WJ, Burton JH, Bock AJ (2001) Intravenous etomidate for procedural sedation in emergency department patients. *Acad Emerg Med* 8: 13-18.
6. Ford SR, Maze M, Gaba DM (1991) A comparison of etomidate and thiopental anesthesia for cardioversion. *J Cardiothorac Vasc Anesth* 5: 563-565.
7. Guler A, Satilmis T, Akinci SB, Celebioglu B, Kanbak M (2005) Magnesium sulfate pretreatment reduces myoclonus after etomidate. *Anesth Analg* 101: 705-709.
8. Doenicke AW, Roizen MF, Kugler J, Kroll H, Foss J, et al. (1999) Reducing myoclonus after etomidate. *Anesthesiology* 90: 113-119.
9. Berry JM, Merin RG (1989) Etomidate myoclonus and the open globe. *Anesth Analg* 69: 256-259.
10. Huter L, Schreiber T, Gugel M, Schwarzkopf K (2007) Low dose intravenous midazolam reduces etomidate induced myoclonus: a prospective, randomized study in patients undergoing elective cardioversion. *Anesth Analg* 105: 1298-302
11. Stockham RJ, Stanley TH, Pace NL, Gillmor S, Groen F, et al. (1988) Fentanyl pretreatment modifies anaesthetic induction with etomidate. *Anaesth Intensive Care* 16: 171-176.
12. Isitemiz I, Uzman S, Toptas M, Vahapoglu A, Glu YG, et al. (2014) Prevention of etomidate-induced myoclonus: which is superior: Fentanyl, midazolam, or a combination? A Retrospective comparative study. *Med Sci Monit* 20: 262-267.
13. Do SH, Han SH, Park SH, Kim JH, Hwang JV, et al. (2008) The effect of injection rate on etomidate induced myoclonus. *Korean J Anesth* 55: 305-307.