MEDICAL SCIENCE MONITOR

DRUG CONTROLLED STUDIES

e-ISSN 1643-3750
© Med Sci Monit, 2014; 20: 262-267
DOI: 10.12659/MSM.889833

Received: 2013.09.28
Accepted: 2013.11.28
Published: 2014.02.16

Prevention of etomidate-induced myoclonus: Which is superior: Fentanyl, midazolam, or a combination? A Retrospective comparative study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Ilke Isitemiz
ABCDEF 1 Sinan Uzman
BCDE 1 Mehmet Toptaş
CDEF 1 Ayşe Vahapoglu
DEF 2 Yaşar Gökhan Gül
ABE 1 Ferda Yilmaz Inal
ABE 1 Ibrahim Akkoc

1 Department of Anesthesiology and Reanimation, Haseki Training and Research Hospital, Istanbul, Turkey
2 Department of Anesthesiology and Reanimation, Kosuyolu High Speciality Training and Research Hospital, Istanbul, Turkey

Corresponding Author: Sinan Uzman, e-mail: drsinanuzman@yahoo.com
Source of support: None

Background: In this retrospective comparative study, we aimed to compare the effectiveness of fentanyl, midazolam, and a combination of fentanyl and midazolam to prevent etomidate-induced myoclonus.

Material/Methods: This study was performed based on anesthesia records. Depending on the drugs that would be given before the induction of anesthesia with etomidate, the patients were separated into 4 groups: no pretreatment (Group NP), fentanyl 1 $\mu g \cdot kg^{-1}$ (Group F), midazolam 0.03 $mg \cdot kg^{-1}$ (Group M), and midazolam 0.015 $mg \cdot kg^{-1}$ + fentanyl 0.5 $\mu g \cdot kg^{-1}$ (Group FM). Patients who received the same anesthetic procedure were selected: 2 minutes after intravenous injections of the pretreatment drugs, anesthesia is induced with 0.3 $mg \cdot kg^{-1}$ etomidate injected intravenously over a period of 20–30 seconds. Myoclonic movements are evaluated, which were observed and graded according to clinical severity during the 2 minutes after etomidate injection. The severity of pain due to etomidate injection, mean arterial pressure, heart rate, and adverse effects were also evaluated.

Results: Study results showed that myoclonus incidence was 85%, 40%, 70%, and 25% in Group NP, Group F, Group M, and Group FM, respectively, and were significantly lower in Group F and Group FM.

Conclusions: We conclude that pretreatment with fentanyl or combination of fentanyl and midazolam was effective in preventing etomidate-induced myoclonus.

MeSH Keywords: Myoclonus – chemically induced • Fentanyl • Etomidate • Midazolam

Full-text PDF: http://www.medscimonit.com/download/index/idArt/889833

2404 4 — 25

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Etomidate is a potent hypnotic agent with minimal cardiovascular and respiratory adverse effects, providing better hemodynamic stability compared with other induction agents and not triggering histamine release. Previous studies reported that at 0.3 mg·kg^{-1} induction doses, etomidate does not cause significant alterations in heart rate, systolic, diastolic, and mean arterial pressures, right atrial pressure, systemic and pulmonary vascular resistance, stroke volume, cardiac index, systemic blood flow, and shunt flow in pediatric patients undergoing congenital cardiac shunt surgery and in adults [1–7].

Induction of anesthesia with etomidate results in dose-dependent myoclonus in 50–80% of patients without premedication [8]. In addition to increasing the risk of aspiration in patients with a full stomach, myoclonus may also increase intraocular pressures and cause problems in patients who will undergo open eye surgery [9].

The incidence of myoclonus is reduced by one-half when pretreatment with 100 µg fentanyl 5 minutes before induction of anesthesia is made, but the incidence of apnea is increased [10]. It was shown that midazolam pretreatment decreased myoclonus induced by etomidate, and increasing the dose of midazolam from 0.015 mg·kg^{-1} to 0.05 mg·kg^{-1} did not further decrease the incidence of myoclonus [11,12].

There are no reported comparative studies that have investigated whether fentanyl or midazolam is a better option in the prevention of myoclonus due to etomidate. The aim of this study was to compare the efficacies of fentanyl, midazolam, or their half-dose combinations in preventing myocloni when they were administered prior to induction of anesthesia with etomidate.

Material and Methods

This retrospective comparative study was performed based on anesthesia records over a period of 6 months. Eighty adult patients with ASA I-II physiologic score and who would undergo various operations under general anesthesia were included in the study. Depending on the drugs that would be given before the induction of anesthesia with etomidate, the patients were separated into 4 groups: no pretreatment (Group NP), fentanyl 1 µg/kg (Group F), midazolam 0.03 mg/kg (Group M), and midazolam 0.015 mg/kg + fentanyl 0.5 µg/kg (Group FM).

The incidence of myoclonus in the no pretreatment group (Group NP) was estimated to be 80%, based on previous studies. Power analysis with α=0.05 and β=0.2 for determining the myoclonus frequency under 50% revealed that each group required a minimum of 17 patients. However, each group included 20 patients according to the admission date. The patients who received the same anesthetic procedure were selected: 2 minutes after intravenous injections of the pretreatment drugs (fentanyl, midazolam or combination of both), anesthesia is induced with 0.3 mg/kg etomidate (Etomidate-Lipuro, B. Braun Melsungen AG, D-34209 Melsungen, Germany), injected intravenously over a period of 20–30 seconds. Two minutes after the end of etomidate injection, muscle relaxation with 0.1 mg/kg vecuronium was achieved and endotracheal intubation was performed after another 2 minutes. Following etomidate injection, mask ventilation with 100% O_2 was carried out until intubation. Anesthesia was maintained using 1.5–2.5% concentration of sevoflurane in a mixture of O_2 and air that contained 50% O_2. Patients who took sedative and analgesic drugs within the 24 hours before the operation were excluded from the study.

Myoclonic movements were evaluated, which were observed and graded according to clinical severity during the 2 minutes after etomidate injection: 0=no myoclonus, 1=mild myoclonus (small movements in 1 body segment, such as finger or wrist), 2=moderate (slight movements in 2 or more muscle areas, such as face or shoulder), and 3=severe (intense movements in 2 or more muscle areas, sudden adduction of an extremity). The severity of pain due to etomidate injection was evaluated using a 4-grade scale: 0=no pain, 1=mild (pain reported only when asked), 2=moderate (pain reported without being asked or reported when asked and there were associated behavioral symptoms), and 3=severe (verbal response, grimacing, pulling the arm, tearing in the eyes). Mean arterial pressure (MAP) and heart rate (HR) recordings were evaluated during the time between entrance into the operating room and 5 minutes after intubation. Decreases in peripheral oxygen saturation (SpO_2 <90%), arrhythmia, and other adverse effects were also evaluated.

The data were registered and analyzed using the SPSS 16.0 for Windows software. Chi-square test was used for comparison of categorical data between the groups. The distribution of group means was evaluated with Kolmogorov-Smirnov test, and after they were found to have normal distribution, 1-way analysis of variance was used to compare the hemodynamic parameters between the groups. Hemodynamic parameter changes in the groups relative to the baseline during each measurement period were evaluated using repeated measurements analysis of variance. Tukey HSD and Dunnett tests were used post hoc to determine the groups showing a statistically significant difference. Data are shown as mean ±s.d. or the number of cases. Statistical significance level was accepted as $p<0.05$.

Results

There were no differences between the groups with respect to mean age, weight, height, ASA physiologic score, sex

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Characteristics of the groups.

	Group NP	Group F	Group M	Group FM
Age (years)	42±12	46±12	44±15	44±15
Weight (kg)	78.8±13.1	72.2±15.9	68.1±15.4	74.1±12.8
Height (cm)	167.9±8.7	164.5±7.7	165.4±7.8	169.7±7.8
ASA I/II (n)	16/4	10/10	16/4	13/7
Sex M/F (n)	13/7	16/4	13/7	10/10
Pain n (%)	1 (5)	0 (0)	2 (10)	0 (0)
Pain score	(0–1)	(0–0)	(0–1)	(0–0)

The datas are given as mean ±s.d.

Table 2. The evaluation of myoclonus after etomidate.

	Group NP	Group F	Group M	Group FM
Myoclonus n (%)				
None	3 (15)	12 (60)*	6 (30)	14 (75)$^{\#,\dagger}$
Mild	4 (20)	2 (10)	1 (5)	3 (15)
Moderate	6 (30)	3 (15)	4 (20)	2 (10)
Severe	7 (35)	3 (15)†	9 (45)	1 (5)**,††

* p<0.01; $^{\#}$ p<0.001 (Compared to Group NP); † p<0.05 (Compared to Group M); ** p<0.05 (Compared to Group NP); †† p<0.01 (Compared to Group M).

Table 3. Mean blood pressure (mm Hg).

Time	Group NP	Group F	Group M	Group FM
1	104±14	108±18	105±18	107±13
2	111±18	90±14*,†	107±20	90±19$^{*,\#}$
3	137±29†	129±18†	136±28†	118±26
4	106±33	108±20	113±30	103±20

1: Basal, 2: Immediately before intubation, 3: Two minutes after intubation, 4: Five minutes after intubation. * p<0.001 (Compared to Group NP); $^{\#}$ p<0.01; † p<0.001 (Compared to basal values).

distribution, and injection pain (p>0.05, Table 1). Pretreatment with either fentanyl or fentanyl-midazolam combination decreased the frequency and severity of myoclonic movements arising after anesthesia induction with etomidate (p<0.001 and p<0.05, respectively (Table 2). During the study period, none of the patients had a decrease in peripheral oxygen saturation, arrhythmia, or any other adverse effects.

Mean arterial pressure measurements after induction were significantly lower in groups F and FM compared to the no pretreatment group (p<0.001). Intragroup comparison showed that MAP had significant reductions to the basal values in Groups F and FM (p<0.001 and p<0.01, respectively). All groups except group FM had significant increases in MAP 2 minutes after intubation (Table 3). Intergroup comparisons showed that mean heart rate values after induction were significantly lower in Groups F and FM compared to Group NP. Intragroup comparisons showed that Group NP had significant elevations which later returned to basal values 5 minutes after intubation (p<0.001). Group F never had significant elevations compared to basal values, whereas group M had significant elevations at all periods (p<0.01 and p<0.001). In group FM, only the HR measurements taken 2 minutes after intubation were significantly higher than basal values (p<0.01, Table 4).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 4. Heart rate (beats per minute).

Time	Group NP	Group F	Group M	Group FM
1	85±14	87±16	78±13	86±13
2	96±21†	79±15*	90±18†	82±14*
3	100±23†	89±16	107±16††	95±13†
4	83±15	81±12	94±18††	89±14

1: Basal, 2: Immediately before intubation, 3: Two minutes after intubation, 4: Five minutes after intubation, * p<0.05 (Compared to Group NP); † p<0.01; †† p<0.001 (Compared to basal values).

Discussion

The results of this study show that the incidence of myoclonus was 85% in the no pretreatment group after etomidate injection; this finding was similar to the others reported in the literature [8,11–19]. The incidence of myoclonus due to etomidate depends on the dosage and speed of injection [8,19]. In healthy volunteers, Doenicke et al. [8] demonstrated that increased doses of etomidate were correlated with the frequency of myocloni, which was 83% with 0.3 mg/kg etomidate. None of the patients had myocloni in doses under 0.05 mg/kg.

Do et al. [19] investigated the effects of slow and rapid etomidate injection rates at 0.3 mg/kg doses on the frequency of myocloni, and observed that 84% of the patients developed myocloni when the drug was administered over a period of 10 seconds, whereas 28% of the patients developed myocloni when the injection was made slowly over a period of 2 minutes. Nyman et al. [13] showed that myocloni developed in 85% of children given 0.3 $mg \cdot kg^{-1}$ intravenous etomidate over a period of 5–10 seconds. In our study, we found similar rates of myocloni when etomidate was given over a period of 20 seconds.

Doenicke showed that after 0.3 mg/kg etomidate, myocloni occurred 80–360 (mean 160) seconds after the injection, and lasted 40–400 (mean 160) seconds [8]. The duration of clinical observation in etomidate-induced myocloni range from 1 to 3 minutes according to various studies. In these studies the incidence of myocloni decreased as the observation period was shortened. Huter et al. [14] applied cardioversion 1 minute after administration of 0.3 mg/kg etomidate, and found that the rate of myoclonus was 50%. Satilmis et al. [20] investigated the efficacy of magnesium sulphate in the prevention of etomidate-induced myoclonus and gave vecuronium to their patients 1 minute after injection of 0.2 mg/kg etomidate. The frequency of myoclonus in patients who received premedication with isotonic saline was 55%. Patients who did not receive premedication and were treated with 0.3 mg/kg etomidate followed by vecuronium 2 and 3 minutes later had 77% and 84% myoclonus rates, respectively [19,20].

In our study we gave the neuromuscular blocker 2 minutes after 0.3 mg/kg etomidate administration, and observed myoclonic movements during this time. The results in our control group were in concordance with other studies having the same observation period length. When the clinical observation period that aims to detect myoclonic movements is shortened, it may result in the suppression of a possibly delayed myoclonus by a neuromuscular blocker and thereby result in lower rates. We believe further studies are necessary to determine the optimal length of observation needed to determine the incidence of myoclonus after etomidate injection.

A study that investigated EEG alterations in patients with etomidate-induced myoclonus stressed the correlation between myoclonus and the increase in delta waves in EEG recordings. In this study, myoclonus was observed to be synchronized with slow and continuous waves on EEG, and it was not a typical seizure. There were no changes except for delta waves in EEG recordings throughout the myoclonic episode. The possible cause of myoclonus during anesthesia induction using etomidate is thought to be subcortical disinhibition. The decreased incidence of myoclonus when using premedication with drugs such as benzodiazepines and fentanyl, which are known to inhibit subcortical neuronal activity, supports this hypothesis [8].

Fentanyl is a μ-opioid receptor antagonist that causes dose-dependent analgesia, respiratory depression, and sedation [21]. The inhibitory effects of midazolam on the central nervous system act through $GABA_A$ receptors [22]. The site of action where fentanyl and midazolam prevent the myoclonus occurring after etomidate injection is not clear [8,14]. However, the prevention of myoclonus by fentanyl and midazolam is a result of inhibition in the central nervous system, although their actions are mediated by different receptors.

In our study, fentanyl and midazolam combination was more effective in the prevention of myoclonus compared to use of either drug alone. We observed that the myoclonus rate decreased to 40% (8/20) in the group that received 1 μg/kg fentanyl before anesthesia induction with etomidate, and to 25% (6/20) in the group that received both 0.5 μg/kg fentanyl and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

0.015 mg/kg midazolam. We also found that 0.03 mg/kg midazolam was inadequate for preventing myoclonus. Although the frequency of myocloni was lower in the group in which fentanyl and midazolam were used together compared to the use of either drug alone, we found that they had no additive or synergistic effect. It has been shown that midazolam and fentanyl display a synergy when used together [23]. However, in the fentanyl+midazolam combination, the use of half the dosage of the drugs compared to when either of them was applied alone can explain why we saw no additive or synergistic effect.

Stocham et al. [10] reported that premedication with fentanyl decreased etomidate-induced myoclonus in a dose-dependent manner, but it increased the risk of apnea. 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%. Giese et al. [24] reported that premedication with 100 µg fentanyl significantly decreased the rate of etomidate-induced myoclonus; however, it introduced the risk of respiratory depression.

Similarly, the rate of myoclonus in our patients premedicated with 1 µg/kg fentanyl was 40%, but none of our patients sustained any episodes of apnea or desaturation. The mean fentanyl dose in our study was 72±16 µg. Myoclonus rates in studies using 100 µg fentanyl and in our study were not different, and we believe that lower doses of fentanyl in our study prevented apneic episodes.

Our results show that 0.03 mg/kg midazolam was not effective in preventing myocloni. The rate of myoclonus was 60% in patients who were treated with midazolam.

Huter et al. [14] reported that in patients undergoing elective cardioversion, 0.015 mg/kg midazolam pretreatment 90 seconds prior to anesthesia induction with 0.3 mg/kg etomidate provided significant reduction in the frequency of myocloni compared to the control group (10% *vs.* 50%). Huter et al. used a shorter observation period (1 minute) than our study, and most of their patients were under magnesium treatment, which account for the difference. Schwarzkopf et al. [11] showed that 0.015 mg/kg midazolam significantly reduced the rate of myoclonus compared to the control group (20% *vs.* 90%). Premedication with oral midazolam and shorter observation period (1 minute) for myoclonus, in contrast to our study, may be the causes for lower incidence. Hwang et al. [12] found that 0.05 mg/kg midazolam pretreatment given 60 seconds prior to induction with 0.3 mg/kg etomidate reduced the rate of myoclonus to 17%, which was 77% in the control group using placebo. The higher dose used in our study may be one of the causes. We therefore conclude that the efficacy of midazolam in prevention of etomidate-induced myoclonus may be correlated with dose, and studies that are better standardized in that aspect are needed.

High osmotic pressure in the etomidate formulation is thought to cause injection pain [25]. The injection pain is reported to be significantly less in lipid-emulsified etomidate compared to etomidate dissolved in propylene glycol [5,13]. We found the injection pain rate of the lipid solution was 0–10%, which is similar in results in the literature.

During evaluation of the hemodynamic effects of etomidate, the control group was also analyzed to exclude the influences of study drugs used in premedication. The results show that etomidate did not cause a significant difference in hemodynamic stability during anesthesia induction. Although the increase in HR was statistically significant, the difference was less than 15% compared to basal values. These findings correlate with those of previous studies [1–7].

The absence of any recording of the onset time of myoclonus within the 2-minute observation period and of its duration was a limiting factor for our study. Studies that will enable investigation of the onset time and duration of myoclonus after etomidate injection may provide us with useful information on the optimal pretreatment time.

Conclusions

We found that both the combination of 0.5 µg/kg fentanyl with 0.015 mg/kg midazolam and 1 µg/kg fentanyl alone were effective in the prevention of myocloni caused by anesthesia induction with etomidate and observed in high rates in patients without premedication. Premedication with 0.03 mg/kg midazolam alone was insufficient for the prevention of myoclonus.

References:

1. Ouedraogo N, Roux E, Forestier F et al: Effects of intravenous anesthetics on normal and passively sensitized human isolated airway smooth muscle. Anesthesiology, 1998; 88(2): 317–26
2. Yeung JK, Zed PJ: A review of etomidate for rapid sequence intubation in the emergency department. CJEM, 2002; 4(3): 194–98
3. Baird CR, Hay AW, McKeown DW, Ray DC: Rapid sequence induction in the emergency department: induction drug and outcome of patients admitted to the intensive care unit. Emerg Med J, 2009; 26(8): 576–79
4. Reich DL, Hossain S, Krol M et al: Predictors of hypotension after induction of general anesthesia. Anesth Analg, 2005; 101(3): 622–28

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

5. Malinowska-Zaprzałka M, Wojewódzka M, Dryl D et al: Hemodynamic effect of propofol in enalapril-treated hypertensive patients during induction of general anesthesia. Pharmacol Rep, 2005; 57(5): 675–78
6. Bergen JM, Smith DC: A review of etomidate for rapid sequence intubation in the emergency department. J Emerg Med, 1997; 15(2): 221–30
7. Dhawan N, Chauhan S, Kothari SS et al: Hemodynamic Responses to Etomidate in Pediatric Patients with Congenital Cardiac Shunt Lesions. J Cardiothorac Vasc Anesth, 2010; 24(5): 802–7
8. Doenicke AW, Roizen MF, Kugler J et al: Reducing myoclonus after etomidate. Anesthesiology, 1999; 90(1): 113–19
9. Berry JM, Merin RG: Etomidate myoclonus and the open globe. Anesth Analg, 1989; 69: 256–59
10. Stockham RJ, Stanley TH, Pace NL et al: Fentanyl pretreatment modifies anaesthetic induction with etomidate. Anaesth Intensive Care, 1988; 16: 171–76
11. Schwarzkopf KR, Hueter L, Simon M, Fritz HG: Midazolam pretreatment reduces etomidate-induced myoclonic movements. Anaesth Intensive Care, 2003; 31(1): 18–20
12. Hwang JY, Kim JH, Oh AY et al: A comparison of midazolam with remifentanil for the prevention of myoclonic movements following etomidate injection. J Int Med Res, 2008; 36(1): 17–22
13. Nyman Y, Von Hofsten K, Palm C et al: Etomidate-Lipuro is associated with considerably less injection pain in children compared with propofol with added lidocaine. Br J Anaesth, 2006; 97(4): 536–39
14. Hüter L, Schreiber T, Gugel M, Schwarzkopf K: Low-dose intravenous midazolam reduces etomidate-induced myoclonus: a prospective, randomized study in patients undergoing elective cardioversion. Anesth Analg, 2007; 105(5): 1298–302
15. Hueter L, Schwarzkopf K, Simon M et al: Pretreatment with sufentanil reduces myoclonus after etomidate. Acta Anaesthesiol Scand, 2003; 47(4): 482–84
16. Guler A, Satilmis T, Akinci SB et al: Magnesium sulfate pretreatment reduces myoclonus after etomidate. Anesth Analg, 2005; 101(3): 705–9
17. Mizrak A, Koruk S, Bilgi M et al: Pretreatment with dexmedetomidine or thiopental decreases myoclonus after etomidate: a randomized, double-blind controlled trial. J Surg Res, 2010; 159(1): e11–16
18. Gultop F, Akkaya T, Bedirli N, Gumus H: Lidocaine pretreatment reduces the frequency and severity of myoclonus induced by etomidate. J Anesth, 2010; 24(2): 300–2
19. Do SH, Han SH, Park SH et al: The effect of injection rate on etomidate-induced myoclonus. Korean J Anesthesiol, 2008; 55(3): 305–7
20. Satılmıs T Guler A, Pamuk AG et al: The comparison of different doses of magnesium sulfate to prevent myclonus after etomidate induction. J Turk Anaesth Int Care, 2010; 38(3): 184–89
21. Pasternak GW: Preclinical pharmacology and opioid combinations. Pain Med, 2012; 13(s1): S4–S11
22. White PF, Eng MR: Intravenous anesthetics. In: Barash PG, Cullen BF, Stoelting RK et al. (eds.), Clinical anesthesia. 6th ed. Philadelphia: Lippincott Williams and Wilkins, 2009; 444–65
23. Hendrickx JF, Eger EI II, Sonner JM, Shafer SL: Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg, 2008; 107(2): 494–506
24. Giese JL, Stockham RJ, Stanley TH et al: Etomidate versus thiopental for induction of anesthesia. Anesth Analg, 1985; 64: 871–76
25. Doenicke AW, Roizen MF, Hoernecke R et al: Solvent for etomidate may cause pain and adverse effects. Br J Anesth, 1999; 83(3): 464–66

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]