

# การป้องกันกล้ามเนื้อกระตุกโดยใช้ยา Midazolam ในขนาดต่ำนำสลบร่วมกับยา Etomidate

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## Prevention of Etomidate-Induced Myoclonic Movement After Midazolam Co-Induction with Low-Dose Etomidate.

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### บทคัดย่อ:

ภาวะกล้ามเนื้อกระตุกเป็นอาการข้างเคียงที่พบบ่อยจากการใช้ยา etomidate นำสลบ  
วัตถุประสงค์: เพื่อศึกษาผลการใช้ยา midazolam ต่ออุบัติการณ์และระดับความรุนแรงของการเกิดภาวะ  
กล้ามเนื้อกระตุกจากยา etomidate

วัสดุและวิธีการ: ผู้ป่วย American Society of Anesthesiologists ระดับ 1-2 จำนวน 112 ราย แบ่งออกเป็น  
4 กลุ่ม โดยวิธีสุ่มให้ได้รับยา midazolam 0.03 มก./กก. นำสลบร่วมกับ etomidate 0.3 และ 0.15 มก./กก.  
เปรียบเทียบกับกรนำสลบด้วยยาหลอก ร่วมกับ etomidate 0.3 และ 0.15 มก./กก. หลังจากนั้นบันทึกอาการ  
กล้ามเนื้อกระตุกที่เกิดขึ้น (ระดับคะแนน 0-3) ระยะเวลาการนำสลบ และสัญญาณชีพ

ผลการศึกษา: อุบัติการณ์ของกล้ามเนื้อกระตุกในแต่ละกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ โดยร้อยละ  
60 ของผู้ป่วยในกลุ่ม midazolam 0.03 มก./กก. นำสลบร่วมกับ etomidate 0.15 มก./กก. เกิดกล้ามเนื้อ  
กระตุก ส่วนร้อยละ 78, 89 และ 77 ในกลุ่ม midazolam 0.03 มก./กก. นำสลบร่วมกับ etomidate 0.3 มก./  
กก., กลุ่ม etomidate 0.3 และ 0.15 มก./กก. มีอาการตามลำดับ ระยะเวลาการนำสลบในกลุ่มที่ใช้ยา midazoam  
ร่วมกับ etomidate ขนาดต่ำไม่แตกต่างจากกลุ่มอื่นๆ

ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ อ.หาดใหญ่ จ.สงขลา 90110

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**สรุป:** อุบัติการณ์การเกิดกล้ามเนื้อกระตุกจากการใช้ midazolam นำสลบร่วมกับ etomidate 0.15 มก./กก. ลดลง แต่ไม่มีนัยสำคัญทางสถิติ

**คำสำคัญ:** กล้ามเนื้อกระตุก, นำสลบ, มิดาโซแลม, อิโตมิเดต

## Abstract:

**Background:** During the induction of anesthesia with etomidate, myoclonic movements are a common problem.

**Objective:** To compare the effect of midazolam on the incidence and severity of myoclonic movement from etomidate induction.

**Materials and methods:** One hundred and twelve patients, American Society of Anesthesiologists class I-II, were randomly assigned in a double-blind fashion into 4 groups: 0.03 mg/kg of midazolam with 0.3, 0.15 mg/kg of etomidate, and placebo with 0.3, 0.15 mg/kg of etomidate. The myoclonic movements were blindly observed on a scale of 0 to 3. The onset of hypnosis and hemodynamic changes were monitored during the operative period.

**Results:** The incidence of myoclonus was not significantly different between groups. Seventeen in 28 patients (60%) in the 0.03 mg/kg of midazolam with 0.15 mg/kg of etomidate group had myoclonic movement, whereas 22 patients (78%) in the 0.03 mg/kg of midazolam with 0.3 mg/kg of etomidate group, 25 patients (89%) and 21 patients (77%) in the 0.3 and 0.15 mg/kg etomidate group experienced such movement. The onset of induction in the low dose etomidate with midazolam co-induction group was not significantly different from the conventional dose of etomidate.

**Conclusion:** Pretreatment with midazolam lowered the incidence of myoclonic movement during induction with 0.15 mg/kg of etomidate but the reduction was not statistically significant.

**Key words:** etomidate, induction, midazolam, myoclonic movement

## Introduction

Etomidate, an imidazole derivative induction agent, has attractive properties including hemodynamic stability, minimal respiratory depression, and pharmacokinetics enabling rapid recovery following either a single dose or continuous-infusion administration. These beneficial effects have led to widespread use of etomidate for induction in hemodynamically unstable patients.<sup>1,2</sup>

However, myoclonic movement was found to be a common problem during anesthesia induction with etomidate with an incidence of approximately 70-90% in premedicated patients.<sup>1,3-8</sup>

Myoclonic movement after etomidate can be reduced by pretreatment with various drugs including fentanyl, remifentanyl, sufentanyl, and magnesium.<sup>5,7,9-11</sup> Previous study also demonstrated that pretreatment with small doses of etomidate

prior to the induction dose decreased the incidence and intensity of myoclonus.<sup>8</sup>

Pretreatment with benzodiazepines such as diazepam or flunitrazepam failed to prevent etomidate-induced myoclonic movement.<sup>9-11</sup> Schwarzkopf et al.<sup>12</sup> showed that low-dose, intravenous midazolam for co-induction can significantly reduce myoclonus in premedicated patients. Nevertheless, even with these medications, myoclonic movement still occurred at the reported incidence rate of 7-50%. Additionally, the effect of co-induction with midazolam in non-premedicated patients to etomidate-induced myoclonic movement was a few.<sup>13</sup> Although many studies related to midazolam co-induction with propofol showed a significant reduction in the dose of propofol required for induction.<sup>14-19</sup> Information on midazolam co-induction with a decreased dose of etomidate is still lacking.

Therefore, the purpose of this study was to compare the effect of midazolam on the incidence and severity of myoclonic movement during two different doses of etomidate induction.

## Materials and methods

With the approval of the Institutional Ethics Committee, a prospective, randomized, double-blind study was performed from July 2007 - June 2009. After obtaining written informed consent from the patients, 112 American Society of Anesthesiologists (ASA) physical status I-II patients aged 18-60 years who were scheduled for elective surgery under general anesthesia were included in the study. Patients with neurologic diseases, hemodynamic instability (such as hypovolemia, septic or cardiogenic shock), at risk of pulmonary aspiration, having a drug allergy or

those who received benzodiazepines within the previous 24 hours were excluded. None of the patients were premedicated. At the operating theater, 7 ml/kg of isotonic saline was completely infused prior to induction in every patient. The heart rate, non-invasive blood pressure, electrocardiography and oxygenation were monitored during the operative period.

Patients were allocated to one of four groups by computer-generated randomization (n=28 in each group): 0.3 mg/kg of etomidate<sup>7,10-13</sup> with 0.03 mg/kg of midazolam (ME<sub>1</sub> group), 0.3 mg/kg of etomidate with a placebo (E<sub>1</sub> group), 0.15 mg/kg of etomidate<sup>2,6</sup> with 0.03 mg/kg of midazolam (ME<sub>2</sub> group) or 0.15 mg/kg of etomidate with a placebo (E<sub>2</sub> group). Normal saline was used for the placebo in E<sub>1</sub> and E<sub>2</sub> groups. Etomidate (Etomidate-Lipuro®, B. Braun Melsungen, Melsungen, Germany) was mixed with normal saline to a total of 10 ml. The solution of induction agents was prepared by a nurse anesthetist not involved during the induction. The anesthesiologist who performed the induction and the patients were not aware of the group allocation.

Five minutes after receiving intravenous midazolam (Dormicum®, F-Hoffmann-La Roche, Basel, Switzerland) diluted in normal saline (3 ml) or the placebo at the same volume, patients received a bolus of etomidate intravenously for 10 seconds as the induction. Other sedative drugs were not allowed during the induction. Time to loss of eyelash reflex was recorded as the onset of induction in all groups. An additional dosage of etomidate was given if clinically necessary.

After loss of eyelash reflex, all patients were continuously observed for two minutes by

an anesthesiologist who was blinded to the identity of the drugs. Myoclonic movement was defined as any abnormal muscle movements. The intensity was graded clinically as 0 = no myoclonic movement, 1 = mild myoclonic movement (movement of fingers, hands or feet), 2 = moderate myoclonic movement (movement of arms or legs), and 3 = severe myoclonic movement (tonic-clonic movement of extremities, needing restraint). Two minutes after etomidate induction, 1.5 µg/kg of fentanyl and 0.1 mg/kg of vecuronium were given to facilitate endotracheal intubation. After intubation and completely recording myoclonic movement, 1-2 mg of midazolam was administered intravenously to prevent intra-operative awareness in E<sub>1</sub> and E<sub>2</sub> groups.

### Statistical analysis

The incidence of myoclonus in the control group (E<sub>1</sub> group) was expected to be 80% based on a previous study.<sup>7</sup> A minimum of 28 patients in each group were required in order to detect a 50% difference in the incidence of myoclonic movement at a significance level of 95% and a power of 80%. Data are shown as the number or the mean±SD (standard deviation). Statistical analyses were performed with program R version 2.7. Pearson chi-square test and analyses of variance were used as appropriate. For all statistical tests, a p-value < 0.05 was considered as statistically significant.

### Results

A total of 112 patients were enrolled; 28 in each group. Two patients were excluded (one

in group ME<sub>1</sub> and one in group E<sub>2</sub>) because of incomplete data. All four groups were comparable with respect to age, gender, weight, height, body mass index, ASA physical status, baseline systolic, mean, diastolic arterial pressure and heart rate (Table 1).

The incidence of myoclonus was not significantly different between groups. Seventeen in 28 patients (60%) in the ME<sub>2</sub> group had myoclonic movement, whereas 25 of 28 patients (89%) in the E<sub>1</sub> group, 22 of 27 patients (78%) in the ME<sub>1</sub> group, 21 of 27 patients (77%) in the E<sub>2</sub> group experienced such movement (Table 2). Further analysis to compare the number of patients who had mild and no myoclonic movement to those with moderate and severe movement, mild-to-moderate and no myoclonus to severe movement, and no myoclonus to movement with any grading were not found to be significantly different (p-value = 0.18, 0.69, and 0.07 respectively) (data not shown). The time to loss of consciousness in the E<sub>2</sub> group was significantly longer than in the other groups (p<0.05). None of the patients in the ME<sub>1</sub> and E<sub>1</sub> group received more supplement doses of etomidate, whereas eight patients in the E<sub>2</sub> group, and only one patient in the ME<sub>2</sub> group were given an additional doses (p<0.05).

At two minutes after induction, mean arterial pressure was significantly different between the groups (p=0.035) (Figure 1). Heart rates were similar among the groups except during the intubation period (p=0.043) (Figure 2).

None of the patients reported any awareness during the operative period.

**Table 1** Characteristics of patients receiving etomidate with and without midazolam for induction.

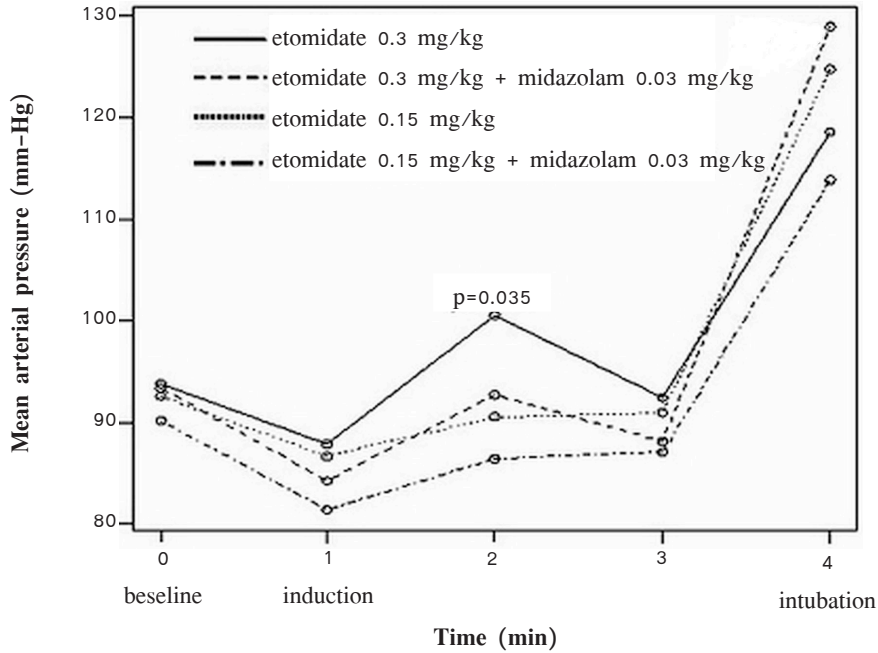
	Group E <sub>1</sub> (n=28)	Group ME <sub>1</sub> (n=27)	Group E <sub>2</sub> (n=27)	Group ME <sub>2</sub> (n=28)	P-value
Age (yr)	39±11	42±11	42±12	41±11	0.79
Sex:					
F/M	18/10	18/9	18/9	19/9	0.95
Weight (kg)	57±8	58±10	55±10	57±8	0.68
Height (cm)	159±7	158±7	158±11	158±8	0.89
BMI (kg/m <sup>2</sup> )	22±4	23±4	22±3	23±3	0.87
ASA class I/II	8/20	7/20	6/21	12/16	0.34

Group E<sub>1</sub> = etomidate 0.3 mg/kg, group ME<sub>1</sub> = etomidate 0.3 mg/kg with midazolam 0.03 mg/kg,  
group E<sub>2</sub> = etomidate 0.15 mg/kg, group ME<sub>2</sub> = etomidate 0.15 mg/kg with midazolam 0.03 mg/kg.

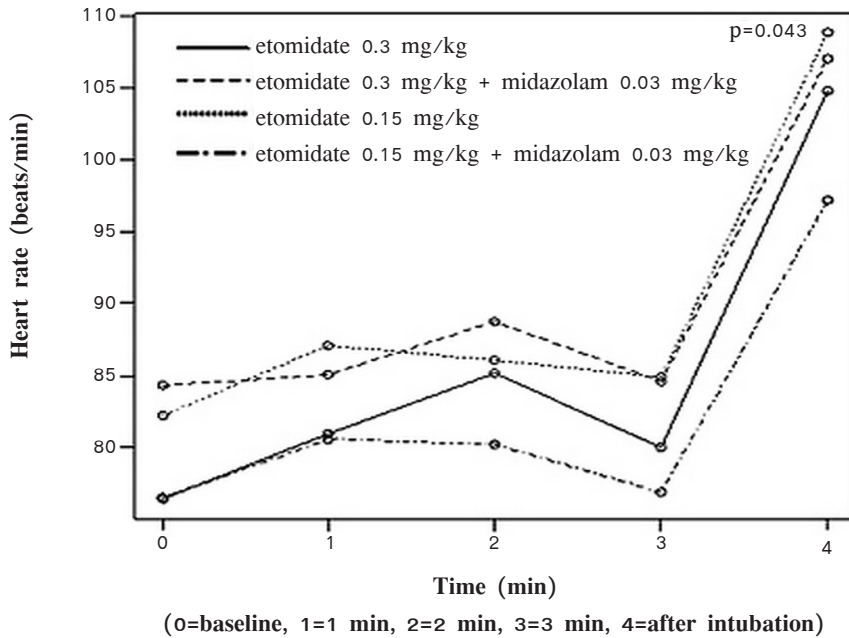
**Table 2** Myoclonic movement, onset of hypnosis after induction and supplemental dose of etomidate between groups. Values are number or mean±SD

	Group E <sub>1</sub> (n=28)	Group ME <sub>1</sub> (n=27)	Group E <sub>2</sub> (n=27)	Group ME <sub>2</sub> (n=28)	P-value
Grade 0	3	5	6	11	0.39
Grade 1	6	6	7	6	
Grade 2	9	10	7	4	
Grade 3	10	6	7	7	
Induction time (sec)	22±7	16±7	64±46	26±23	<0.05
Supplement dose of etomidate	0	0	8	1	<0.05

Group E<sub>1</sub> = etomidate 0.3 mg/kg, group ME<sub>1</sub> = etomidate 0.3 mg/kg with midazolam 0.03 mg/kg,  
group E<sub>2</sub> = etomidate 0.15 mg/kg, group ME<sub>2</sub> = etomidate 0.15 mg/kg with midazolam 0.03 mg/kg.



**Figure 1** Changes in mean arterial pressure (mmHg) between 4 different groups at baseline and every 1 minute from induction until intubation. Mean  $\pm$  standard deviation (SD).



**Figure 2** Changes in heart rate (bpm) between 4 different groups at baseline and every 1 minute from induction until intubation. Mean  $\pm$  standard deviation (SD).

## Discussion

Our study demonstrates that the incidence of myoclonic movement caused by etomidate is high. Most of the patients experienced some degree of myoclonus. The dose of 0.3 mg/kg of etomidate produced 89% myoclonic movement. This is supported by a previous report of myoclonus in non-premedicated patients when anesthesia was induced with etomidate.<sup>13</sup>

Of all the benzodiazepines, diazepam and midazolam have been investigated to diminish the incidence and the severity of etomidate induced myoclonus.<sup>11-13</sup> Schwarzkopf et al. and Hueter et al. showed that the effects of 0.015 mg/kg of midazolam being administered intravenously 90 seconds before etomidate injection could reduce such an effect. Because the patients in this study were not premedicated, the dose of midazolam was increased to 0.03 mg/kg intravenously. However, by increasing the dose of midazolam, the present study failed to support the effects of midazolam co-induction with both 0.15 and 0.3 mg/kg doses of etomidate which had the incidence rate of 60 and 78% respectively. The reason for this difference in the result is not clear. The explanation may include that in our study midazolam was injected 5 minutes before the etomidate administration to ensure an adequate interval for the onset of midazolam but this time delay might not have allowed the peak effect of premedication. On the other hand, etomidate was administered 90 seconds following midazolam pre-treatment in the previous reports.<sup>12,13</sup> Additionally, we observed the clinical occurrence of myoclonic movements for at least two minutes after the etomidate injection, whereas the observa-

tion period was only one minute in previous reports.<sup>5-7,12,13</sup> Our longer observation time probably increased the chance of detecting such movements.

The myoclonic movement was also shown to be related to other factors such as the dose of etomidate, speed of injection and the patient's age. Korttila et al.<sup>11</sup> reported the correlation between the involuntary movements from etomidate and increasing age, but the patients' age in our study were similar between groups. Doenicke et al.<sup>8</sup> found that etomidate-induced myoclonus was dose related. None of the patients who received 0.025 and 0.05 mg/kg of etomidate had myoclonus, however, 0.075 mg/kg of etomidate caused such movements in men. In our study, we did not find a different incidence of myoclonic movement between low (0.015 mg/kg) and conventional (0.03 mg/kg) doses of etomidate. The difference in the speed of etomidate injection might produce more effect than the dosage and may partially explain the difference of previous study and our results. We injected etomidate in a bolus manner over 10 seconds intravenously, whereas Kelsaka et al.<sup>5</sup> injected etomidate over 60 seconds. Slow injection of etomidate may behave like a small priming dose which has been demonstrated to reduce the incidence of myoclonic movements.<sup>8</sup> This may also be another reason for why we observed a slightly lower incidence of myoclonus following midazolam pre-treatment.

The problem of myoclonus associated with etomidate has been recognized for many years. This adverse reaction of etomidate may be detrimental in patients with open-globe injury and in emergency non-fasting conditions.<sup>5,8</sup> This clinical

adverse effect may be mild and transient, involving only a few axial muscle groups or it may resemble generalized seizure activity. The mechanism of etomidate-induced myoclonic movements remains unclear, but it may related to subcortical disinhibition like the phenomenon of restless legs during normal human sleep and is not generated by an epileptic foci.<sup>8</sup> Using a concentration-dependent method, Liu et al. also proposed that the N-Methyl D-aspartate-gated current reduction by sodium thiopental caused the dissociation of the prefrontal cortical pyramidal neuron.<sup>20</sup> The actions of etomidate and midazolam on different Gamma aminobutyric acid (GABA) receptor subunits may play a role in potentiating or modifying the effects that produce myoclonus.

The use of etomidate for anesthesia has proven to be safe and effective in most clinical settings with minimal side effects on cardiac performance. Our data indicated that the cardiovascular effects of midazolam co-induction with etomidate were not clinically different even though there were significant differences in some values. At two minutes after induction, mean arterial pressure was significantly different between groups. Heart rates were similar among the groups except during the intubation period.

The major limitation of this study is the small sample size which may not be adequate to detect the difference in the incidence. Future studies may be undertaken utilizing larger patient groups to strengthen the results of the present study. Additionally, we did not use cerebral function monitoring, such as Bispectral Index, to guide the adequate of depth of anesthesia during the induction period, especially in the

low dose etomidate groups. The intraoperative awareness in this study, therefore, may be underdiagnosed because it was only self-reported from the patients.

## Conclusion

**In conclusion, the findings of our study showed that co-induction of 0.03 mg/kg of midazolam with a low dose of etomidate resulted in a lower, but nonsignificant, tendency to reduce myoclonic movements without delaying the onset of induction when anesthesia was induced with etomidate.**

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