

Etomidate Should be Used Carefully for Emergent Endotracheal Intubation in Patients with Septic Shock

Etomidate and midazolam are the most popular drugs among the induction agents for emergent endotracheal intubation. The purpose of this study was to compare the incidence of adrenal insufficiency and mortality between the septic shock patients who received etomidate (ETM group) and those who received midazolam (MDZ group). Between November 2004 and September 2006, 65 patients were analyzed in this study. The hospital mortality rate was 36% in the ETM group (n=25) and 50% in the MDZ group (n=40), which was not statistically significant ($p=0.269$). The incidence of relative adrenal insufficiency was significantly higher in the ETM group than in the MDZ group (84% and 48%, respectively; $p=0.003$). On multivariate analysis, the use of etomidate was the only significant factor affecting the incidence of relative adrenal insufficiency (odds ratio, 5.59; 95% confidence interval, 1.61-19.4). In conclusion, we think that physicians who treat patients with septic shock should be aware that etomidate can cause adrenal insufficiency, and should start corticosteroids if etomidate is administered.

Key Words : Etomidate; Midazolam; Intubation; Adrenal Insufficiency; Shock, Septic

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INTRODUCTION

Emergent endotracheal intubation is a common procedure performed for the stabilization of critically ill patients and the majority of these patients will require an induction agent for rapid-sequence intubation (RSI). Etomidate and midazolam are the most popular drugs among the induction agents (1).

Midazolam, however, can cause hypotension when used in doses to produce sedation for intubation. It also has a broad dose-response relationship that makes dosing inconsistent and unpredictable (2, 3). The occurrence of hypotension is associated with significant mortality and morbidity in critically ill patients (4, 5).

On the other hand, etomidate has become the induction agent of choice for RSI due to its rapid onset of action and recovery and minimal adverse cardiovascular and respiratory effects (6, 7). However, etomidate is known to inhibit adrenal mitochondrial hydroxylase activity, resulting in adrenocortical dysfunction after administration by even though a single bolus (8, 9). This disadvantage of etomidate can restrict its use in patients prone to develop relative adrenal insufficiency such as severe sepsis and septic shock (10-12).

The purpose of this study was to compare the incidence of adrenal insufficiency and mortality between the patients with severe sepsis and septic shock who received etomidate as an induction agent during RSI and those who received midazolam.

MATERIALS AND METHODS

In this retrospective study, we first identified 152 consecutive patients who had received cosyntropin stimulation test (CST) and endotracheal intubation at Seoul National University Hospital between November 2004 and September 2006.

The medical records of these patients were reviewed and we included the patients in this study if they met all of the following criteria: 1) age older than 18 yr, 2) severe sepsis or septic shock, 3) induction agents administered before emergent endotracheal intubation, and 4) CST performed within 24 hr after the administration of the induction agents. Patients were excluded if they had received corticosteroids or ketoconazole within 1 month prior the CST, or if they had an adrenal or pituitary disorder.

Severe sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Committee criteria (13). CST was performed, as usual, using 250 μ g of tetracosactin (Synacthen™, Ciba, England) and relative adrenal insufficiency was defined as an increment of 9 μ g/dL or less after CST (14).

Data collected included demographics, the dosage of induction agents and neuromuscular blockers, the time interval between the induction agent administration and the CST, Acute Physiology and Chronic Health Evaluation (APACHE) II score on the 1st day of intensive care unit (ICU) admission, the results of CST, the length of ICU stay, hospital mor-

tality, and 1-, 3-, and 6-month mortality.

Patients were divided into those who received etomidate (ETM group) and those who received midazolam (MDZ group). The Student's t-test was used for comparisons of normally distributed continuous variables between two groups, and binominal variables were analyzed with χ^2 test or Fisher's exact test, as appropriated. Predicting factors for mortality and relative adrenal insufficiency were evaluated by univariate analysis. The factor(s) with a *p* value <0.2 by univariate analysis would be taken to multivariate logistic regression analysis. Statistical analyses were carried out with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, U.S.A.) and a *p* value <0.05 was considered statistically significant.

This study was approved by the Institutional Review Board at Seoul National University Hospital.

RESULTS

Of the 152 consecutive patients who had CST and endotracheal intubation, 56 were excluded. Fifty patients had the CST done before or more than 24 hr after the adminis-

Table 1. Baseline characteristics of study patients by induction agents*

Variables	ETM (n=25)	MDZ (n=40)	<i>p</i> value
Age (yr)	63.3 ± 14.1	63.8 ± 12.7	0.878
Male, n (%)	14 (56)	33 (83)	0.020
Body weight (kg)	59.0 ± 17.2	54.0 ± 11.2	0.163
Classification of sepsis (n)			
Septic shock	25	38	0.887
Severe sepsis	0	2	NA
Site of infection, n (%)			
Respiratory tract	15 (60)	30 (75)	0.583
Intraabdominal	4 (16)	6 (15)	0.913
Others	6 (24)	4 (10)	0.083
Pre-existing malignancy, n (%)	5 (20)	12 (30)	0.372
APACHE II score	27.5 ± 6.4	26.4 ± 5.6	0.479
Systolic blood pressure (mmHg)	95.1 ± 17.2	93.8 ± 19.8	0.794
Diastolic blood pressure (mmHg)	44.7 ± 11.6	46.5 ± 13.1	0.575
Mean arterial pressure (mmHg)	61.5 ± 12.6	62.2 ± 14.1	0.822
Heart rate (bpm)	99.8 ± 23.6	99.6 ± 27.7	0.980
Body temperature (°C)	36.7 ± 1.4	36.7 ± 1.3	0.869
Induction agent dose (mg/kg)	0.31 ± 0.08	0.07 ± 0.02	NA
Use of neuromuscular blocker, n (%)	21 (84)	35 (88)	0.691
Glucocorticoids replacement therapy, n (%)	23 (92)	30 (75)	0.109
Interval from induction agent to CST (hr)	9.0 ± 6.7	11.6 ± 6.8	0.147
Baseline cortisol level (μg/dL)	20.4 ± 12.8	20.6 ± 10.3	0.934

*, Plus-minus values are means ± SD.

ETM, patients who received etomidate as an induction agent; MDZ, patients who received midazolam as an induction agent. CST, cosyntrophin stimulation test; NA, not applicable.

tration of the induction agents, and 6 patients had other types of shock (5 cardiogenic shock and 1 hemorrhagic shock).

Among the 96 patients met the inclusion criteria, 27 patients were excluded for having received corticosteroids, and 4 patients had pituitary tumor. Finally 65 patients were analyzed in this study.

Of the patients, 47 (72%) of patients were male and the mean age of the patients was 64 yr. The mean dose of etomidate given was 0.3 mg/kg and that of midazolam 0.07 mg/kg. The time interval between the induction agent administration and the CST was 10.6 hr and the mean of APACHE II scores was 27. As summarized in Table 1, no significant differences in the baseline characteristics except the male-to-female ratio were found in between the two groups (Table 1).

The overall hospital mortality rate was 45%, while the hospital mortality rate predicted by the APACHE II score was 61%. The hospital mortality rate was 36% in the ETM group (n=25) and 50% in the MDZ group (n=40), which was not statistically significant (*p*=0.269). There were no significant differences in the 1-, 3-, and 6-month mortality between the two groups.

Twelve patients were failed to be intubated at the 1st attempt, and endotracheal intubation was attempted by 1st and 2nd-year residents in all of 12 patients. The overall incidence of relative adrenal insufficiency was 62%. The incidence of relative adrenal insufficiency was significantly higher in the ETM group than that in the MDZ group (84%, 48% respectively; *p*=0.003) (Table 2).

We performed univariate and multivariate analyses to identify significant factor(s) affecting the hospital mortality and the relative adrenal insufficiency. The APACHE II score was the only significant factor affecting the hospital mortality (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.06-1.36) and the use of etomidate was the only significant factor affecting the incidence of relative adrenal insufficiency (OR, 5.59; 95% CI, 1.61-19.4).

Table 2. Clinical outcomes by induction agents*

Variables	ETM (n=25)	MDZ (n=40)	<i>p</i> value
Hospital mortality, n (%)	9 (36)	20 (50)	0.269
1-month mortality, n (%)	8 (32)	17 (43)	0.397
3-month mortality, n (%)	10 (40)	21 (53)	0.326
6-month mortality, n (%)	13 (52)	23 (58)	0.664
Adrenal insufficiency, n (%)	21 (84)	19 (48)	0.003
ICU stay (day)	21.0 ± 17.2	20.8 ± 20.3	0.974
Intubation failure at 1st attempt, n (%)	0	12 (30)	0.002

*, Plus-minus values are means ± SD.

ETM, patients who received etomidate as an induction agent; MDZ, patients who received midazolam as an induction agent.

DISCUSSION

Etomidate and midazolam are the most popular induction agents used during emergent endotracheal intubation, and it is of great concern for physicians treating hemodynamically unstable patients to determine which drug to use when they require the induction agents to facilitate endotracheal intubation.

The aim of the present study was to compare the incidence of adrenal insufficiency and mortality between the septic shock patients who received etomidate and those who received midazolam. As far as we know, there has been no report that compared the clinical outcomes such as the incidence of relative adrenal insufficiency and mortality in the patients with severe sepsis and septic shock who received etomidate and midazolam, two most popular induction agents.

There are few studies that evaluated adrenal insufficiency and hospital mortality between septic shock patients who received etomidate and those who did not. Moreover, these studies had significant drawbacks that they did not mention the severity of septic shock and the time interval from administration of the induction agents to CST, and the use of supplemental corticosteroids (15, 16). These factors can strongly affect the incidence of adrenal insufficiency and hospital mortality.

In accordance with previous studies, we found that 61.5% of our patients had relative adrenal insufficiency (14, 17). Also, the ETM group had a significantly higher incidence of relative adrenal insufficiency than the MDZ group, which reaffirms that etomidate can cause adrenocortical dysfunction (11, 15, 16).

In our study, there were no significant differences in hospital mortality, 1-, 3-, and 6-month mortality between the two groups even though the ETM group had a higher incidence of relative adrenal insufficiency than the MDZ group, which is consistent with previous studies (15, 16).

There are some explanations to these findings. First of all, most of our patients received corticosteroids replacement therapy, which may offset the detrimental effect of adrenal insufficiency. Annane *et al.* demonstrated that in septic shock patients with relative adrenal insufficiency, a 7-day treatment with the combination of hydrocortisone and fludrocortisone was associated with a significant reduction in short-term and long-term mortality (19). In our study, 92% of ETM group and 75% of MDZ group had corticosteroid replacement therapy. Although it was not statistically significant ($p=0.109$), the ETM group had an increased tendency to take glucocorticoids.

Second, although the causal relationship between adrenal insufficiency and mortality has remained open, there may be a potentiality that adrenal insufficiency itself will not be associated with an increased mortality. According to a recent study on the adrenal function in patients with severe sepsis and septic shock, adrenal insufficiency itself did not affect

the hospital mortality (17).

Last, adrenocortical dysfunction caused by etomidate may be transient. Several studies suggest that a single dose of etomidate results in the suppression of adrenal function that lasts at least 1 day in critically ill patients (11, 12, 18), while one prospective randomized study showed that adrenocortical dysfunction resolves within 12 hr of a single bolus dose of etomidate (9). All of the above might have contributed to this finding; however, the authors think corticosteroids replacement therapy would be the main cause that made little difference in mortality.

Another finding to be mentioned in our study was that there was a significantly higher intubation failure rate in the MDZ group than in the ETM group. The successful endotracheal intubation depends on many factors such as patients' airway anatomy, experience and competency of intubators, and appropriate use of drugs and devices.

In the present study, there were no significant differences in body weight, age, and APACHE II score between the patients who were successfully intubated or not at 1st attempt ($p=0.550$ and 0.531 , respectively). Interestingly, endotracheal intubation was attempted by 1st and 2nd-year residents and midazolam was administered in all of 12 patients who failed to be intubated.

As midazolam had been the most popular induction agent and etomidate was introduced to the hospital merely a few years ago, junior doctors would be apt to select midazolam as a sedative of choice. We think the reason why the MDZ group had a significantly higher intubation failure rate was not that use of midazolam, by itself, affected the intubation failure, but that more inexperienced doctors were included in the MDZ group. We could not evaluate anymore the causes of intubation failure because there was not enough of the detailed information about each intubation.

This study had several limitations. It was performed in a single tertiary hospital and had a retrospective study design. The small sample size may account for the absence of statistically significant difference in some of variables including hospital mortality.

Our study showed that etomidate used in patients with severe sepsis and septic shock causes adrenocortical dysfunction, although the mortality was not affected.

In conclusion, physicians who treat patients with severe sepsis and septic shock should be aware that the use of etomidate significantly increases the incidence of relative adrenal insufficiency, and it would be safer to start corticosteroid replacement therapy once etomidate is administered in these patients.

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