

# A Prospective Observational Study of the Effect of Etomidate on Septic Patient Mortality and Length of Stay

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## Abstract

**Objectives:** Etomidate is known to cause adrenal suppression after single-bolus administration. Some studies suggest that when etomidate is used as an induction agent for intubation of septic patients in the emergency department (ED), this adrenal suppression leads to increased mortality, vasopressor requirements, and length of hospital stay. The authors sought to determine differences in the in-hospital mortality and hospital length of stay (LOS) between septic patients given etomidate and patients given alternative or no induction agents for rapid-sequence intubation in our ED.

**Methods:** This was a nonrandomized, prospective observational study of all patients meeting sepsis criteria who were intubated in an ED over a 9-month period. Times of patient presentation, intubation, admission, discharge, and/or death were recorded, as well as the intubation agent used, if any, and corticosteroid use. The authors also recorded relevant laboratory and demographic variables to determine severity of illness using the Mortality in Emergency Department Sepsis (MEDS) score. Mortality and survivor LOS between the patients given etomidate and those given alternative or no induction agents were compared.

**Results:** A total of 106 patients with sepsis were intubated over the study period. Of these, 74 patients received etomidate, while 32 patients received ketamine, benzodiazepines, propofol, or no induction agents. Age in years (median = 78; interquartile range [IQR] = 67 to 83), gender (45% male), MEDS score (median = 13; IQR = 10 to 15), and receipt of supplemental corticosteroids (56%) were statistically similar between the two groups. In-hospital mortality of patients given etomidate (38%; 95% confidence interval [CI] = 28% to 49%) was similar to those receiving alternatives (44%; 95% CI = 28% to 61%). Surviving patients had a median hospital LOS after receiving etomidate of 10 days compared to those receiving alternatives (7.5 days;  $p = 0.08$ ).

**Conclusions:** No statistically significant increase in hospital LOS or mortality in patients given etomidate for rapid-sequence intubation was found. Suggestions that the use of etomidate for intubation in the ED be abandoned are not supported by these data.

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**Keywords:** etomidate, sepsis, adrenal suppression

**A**lthough the use of etomidate for continuous sedation in mechanically ventilated patients was found to have detrimental effects on patient

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mortality shortly after its introduction,<sup>1-4</sup> etomidate continues to be widely used in a single-bolus dose as an induction agent for endotracheal intubation in the emergency department (ED).<sup>5,6</sup> Recently, the safety of using etomidate as an induction agent has come into question, because single-bolus doses of this drug have been shown to cause relative adrenocortical insufficiency.<sup>7-16</sup>

Few studies specifically investigating the clinical outcomes of septic patients treated with etomidate have been published. A retrospective study found an increased mortality rate in septic patients given etomidate.<sup>17</sup> A post hoc analysis of a large prospective study of the effects of hydrocortisone in sepsis found an increased rate of death among patients who received etomidate.<sup>16</sup> A small prospective randomized study of

30 trauma patients found measurable adrenal suppression, as well as increased hospital length of stay (LOS), ventilator days, and intensive care unit (ICU) days in those patients receiving single-bolus doses of etomidate.<sup>18</sup>

To examine outcomes in septic patients in our ED, we sought to determine the difference in in-hospital mortality and hospital LOS between septic patients given etomidate and those given alternative induction agents for rapid-sequence intubation. Specifically, we prospectively followed septic patients intubated in our ED over a 9-month period and compared the outcomes between patients given etomidate and patients given alternative induction agents for intubation. We hypothesized that patients given etomidate would have longer hospital stays and increased mortality when compared to patients given alternative agents.

## METHODS

### Study Design

We conducted a prospective, nonrandomized, observational cohort study from February 2007 to October 2007. This study was approved by the hospital's institutional review board, with a waiver of informed consent.

### Study Setting and Population

This study was conducted at a large tertiary care suburban community hospital with over 85,000 ED visits annually and nearly 700 inpatient beds. We evaluated all patients over the age of 18 years who had 1) two or more systemic inflammatory response syndrome criteria (temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ , heart rate  $> 90$  beats/minute, respiratory rate  $> 20$  breaths/minute, or partial pressure of carbon dioxide [ $\text{PaCO}_2$ ]  $< 32$  mm Hg, white blood cell count  $> 12 \times 10^9$  or  $< 4 \times 10^9/\text{L}$ , or  $> 10\%$  bands); 2) a suspected or documented infection; and 3) intubation performed in our ED.

### Study Protocol

We notified all attending and resident physicians of the study and asked that they alert one of the study coordinators to any septic patients who they intubated. For 5 days each week, we instituted daily monitoring of our electronic tracking board by a research assistant to identify patients potentially meeting our study criteria. To confirm that all potentially eligible patients were included in our study, we obtained weekly records from our Omnicell medication dispensing cabinet to identify all instances in which intubation medications were used.

A standardized abstraction form was created for data collection. These data included patient demographics, induction agent, time of intubation, supplemental steroid use, laboratory results, hospital LOS, and discharge status. We determined the severity of illness by using the Mortality in Emergency Department Sepsis (MEDS) score, which is a prospectively derived and validated scoring system that utilizes data commonly obtainable while the patient is still in the ED.<sup>19</sup>

## Outcome Measures

Our primary outcome was in-hospital mortality, and our secondary outcome was overall hospital LOS, measured in days from ED presentation to hospital discharge.

## Data Analysis

Baseline demographic and clinical characteristics are described using means with 95% confidence intervals (CIs) for normally distributed data and medians with interquartile ranges (IQRs) for nonnormal data. Individual patient encounters served as the units of analysis.

We compared 1) the mortality of each of the two groups with 95% CIs using the Wilson score method, 2) the unadjusted mortality between the two cohorts with the chi-square test, and 3) the LOS of all patients and of surviving patients with the Mann-Whitney U test. We then performed multiple logistic regression modeling to obtain adjusted odds ratios (ORs) for the outcome of death, controlling for measured covariates related to severity of illness, and performed multiple linear regression modeling on the outcome of LOS (using a log-transformation to normalize the data) to examine the effects of these same variables related to severity of illness. To explore multiple potentially significant variables and to identify the subset of variables most associated with our outcomes, we utilized a backward stepwise procedure requiring entry criteria of a significance level of less than 0.05 and removal at significance level of 0.10. Covariates included patient age, vital signs at time of intubation (heart rate, mean arterial blood pressure, temperature, and respiratory rate), gender, use of vasopressors, use of steroids, and MEDS score. To investigate the possibility of nonlinearities that would suggest interactions between predictor variables, we examined plots of residuals against independent predictor variables. All analyses utilized two-sided tests. We considered values of  $p < 0.05$  to be statistically significant for all analyses. Analyses were performed using SPSS Version 15.0 (SPSS Inc., Chicago, IL).

## RESULTS

A total of 106 patients meeting our study criteria were intubated over the 9 months; 74 patients received etomidate and 32 patients received alternative agents. Of the patients who received alternative induction agents, 22 received benzodiazepines, 3 received ketamine, 1 received propofol, 1 received ketamine and benzodiazepine, and 5 did not receive any induction medication prior to intubation.

Baseline characteristics of the patients for each cohort are shown in Table 1. Although a slightly higher proportion of patients not receiving etomidate received supplemental steroids, no statistically significant difference in age, MEDS score, mean arterial pressure, heart rate, gender, use of supplemental steroids, or vasopressor use was seen between cohorts.

### Primary Outcome

In-hospital mortality of patients given etomidate (38%; 95% CI = 28% to 49%) was similar to those receiving alternatives (44%; 95% CI = 28% to 61%). The mortality of patients receiving no induction agent was 20%.

**Table 1**  
Baseline Patient Characteristics, Severity of Illness, and Use of Supplemental Steroids and Vasopressors

	Etomidate (n = 74)	No Etomidate (n = 32)
Age (years)	76 (66–82)	79 (70–85)
MEDS score	13 (10–16)	13 (10–15)
Mean arterial pressure	73 (57–88)	78 (57–97)
Heart rate	104 (79–131)	116 (79–131)
Gender (% male)	46	44
Supplemental steroids	50	69
Vasopressors	58	59

Data are reported as median (IQR) or frequency (%).  
IQR = interquartile range; MEDS = mortality in emergency department sepsis.  
\*No statistically significant differences between cohorts were found in any category.

### Secondary Outcome

Overall hospital LOS for patients who received etomidate was 8 days (IQR = 3 to 13 days) versus 6.5 days (IQR = 3 to 9.75 days) for patients who did not receive etomidate ( $p = 0.18$ ). A total of 46 patients who received etomidate (of 74) survived to discharge, while a total of 18 patients receiving alternative or no induction agents (of 32) survived to discharge. Of patients surviving to hospital discharge, hospital LOS was 10 days (IQR = 7 to 16.25 days) in patients who received etomidate versus 7.5 days (IQR = 4.75 to 10.5 days) in patients who did not receive etomidate ( $p = 0.08$ ).

### Multivariate Analysis

Results of multiple linear regression including potential effects of the additional confounders of patient age, vital signs at time of intubation (heart rate, mean arterial blood pressure, temperature, and respiratory rate), gender, use of vasopressors, use of steroids, and MEDS score on the outcome LOS showed that only the use of vasopressors remained a significant predictor of outcome ( $F = 7.86$ ;  $\beta = 0.47$ ;  $p = 0.008$ ). Results of a multivariate logistic regression analysis controlling for the effect of these same variables on patient mortality showed that only one variable, mean arterial blood pressure, remained a significant predictor of the outcome patient mortality (OR = 1.02; 95% CI 1.001 to 1.05;  $p = 0.04$ ). Because we were limited by the size of our study, and because we did not find suggestions of significant interactions between possible confounders, or have a priori hypotheses predicting interactions, we did not further investigate the effects of interactions between confounders on our outcomes.

### DISCUSSION

Detrimental effects of long-term use of etomidate, described shortly after its introduction, were attributed to its measurable effects on adrenal suppression and resulted in a warning against prolonged infusion being placed in the package insert that cites the “hazards of

prolonged suppression of endogenous cortisol and aldosterone production” (Bedford Laboratories, Bedford, OH).<sup>20</sup> More recently, the use of etomidate as a single bolus dose has been questioned, with an increasing number of authors suggesting that etomidate no longer be used in patients at risk for adrenal insufficiency.<sup>7–9,13,14</sup>

Although the controversy over the possible effects of etomidate continues, strongly conclusive evidence of detrimental effects has not yet been published. A prospective, randomized study of 30 trauma patients found an increase in ICU and hospital LOS, as well as an increase in ventilator days, in patients randomized to etomidate when compared to patients randomized to midazolam; however, the study was unable to utilize blinding of assignment and excluded a large percentage of patients.<sup>18</sup> A recent retrospective analysis of data obtained by the Corticus study group suggests an association of etomidate with worse outcomes in septic patients, with a univariate OR for death of 1.53 (95% CI = 1.06% to 2.26%) in patients given etomidate.<sup>17</sup> More recently, etomidate was found to be associated with reduced response to corticotropin and an increased rate of death at 28 days in a prospective study of the use of hydrocortisone in patients with septic shock.<sup>16</sup>

Our study did not find the significant increase in mortality or hospital LOS that has been postulated by some authors, although our results do suggest the possibility of a trend toward increased hospital LOS, which may serve as an indicator of greater resource requirements for patients given etomidate. Prior studies have suggested adverse effects of etomidate on various endpoints, including reduced plasma cortisol and aldosterone levels, decreased responses to cosyntropin stimulation, and increased vasopressor requirements, lending further plausibility to a link between etomidate use and hospital LOS.<sup>10,12,21</sup> Nevertheless, the lack of statistical significance of our finding does not, at this point, provide convincing evidence that the use of a single-bolus dose of etomidate for intubation in the ED should be abandoned. An ongoing randomized trial at our institution comparing etomidate to midazolam (ClinicalTrials.gov Identifier NCT00441792) will attempt to further quantify this link.

### LIMITATIONS

Although we took steps to assure that all eligible patients over the study period were included in our analysis, our study did not randomize patients to treatments and relied instead on the observation of outcomes that may be influenced by physician choice of intubation agent. The baseline characteristics and severity of illness, as measured by the MEDS score, between the two patient groups were similar; however, additional unmeasured variables, including general clinical appearance, may affect our results. Moreover, despite similar usage of steroids, subsequent care provided to patients may have varied between the two groups in other unmeasured, and potentially biased, ways, particularly since intubating agents were not blinded.

Because this was a single-center study, generalizations to other institutions are limited. The size of our sample likewise limits our ability to detect smaller differences in the outcome of mortality. We did not investigate additional surrogate outcome markers such as length of time for which intubation was required or length of time patients spent in the ICU.

Our results do not appear particularly robust; sensitivity analysis of our data shows that a change of as few as two patients miscategorized by outcome or treatment would result in the gain of statistical significance in the differences we saw in LOS between groups.

## CONCLUSIONS

Patients in our ED given etomidate for rapid sequence intubation and surviving to hospital discharge had a nonstatistically, but potentially clinically significant, increase in median hospital LOS compared to patients given alternative induction agents. We did not find a difference in mortality between our cohorts. Thus, recommendations to discontinue the use of etomidate because of fears of increased mortality may be unwarranted pending the accumulation of further data.

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