A Comparison of the Effects of Etomidate and Midazolam on Hospital Length of Stay in Patients With Suspected Sepsis: A Prospective, Randomized Study

Karis L. Tekwani, MD, Hannah F. Watts, MD, Rolla T. Sweis, PharmD, Kathleen H. Rzechula, RN, Erik B. Kulstad, MS, MD
From the Department of Emergency Medicine, Advocate Christ Medical Center, Oak Lawn, IL.

Study objective: Etomidate, a widely used induction agent for rapid sequence intubation in the emergency department (ED), causes measurable adrenal suppression after a single bolus dose. The clinical significance of this adrenal suppression in patients with sepsis remains controversial. We seek to determine the difference in hospital length of stay between patients with suspected sepsis who receive either etomidate or midazolam during intubation in our ED.

Methods: We performed a prospective, double-blind, randomized study of patients with suspected sepsis who were intubated in our ED during an 18-month period. Eligible patients who were critically ill and were suspected of having sepsis were randomized to receive either etomidate or midazolam before intubation.

Results: A total of 122 patients were enrolled; 59 received midazolam and 63 received etomidate. Two patients in the etomidate group were lost to follow-up. Patient baseline characteristics were similar between groups. There were no significant differences in median hospital length of stay (9.5 versus 7.3 days), ICU length of stay (4.2 versus 3.1 days), or ventilator days (2.8 versus 2.1) between patients who received midazolam and those who received etomidate, respectively. Inhospital mortality was 21 of 59 (36%; 95% confidence interval 24% to 49%) for patients who received midazolam and 26 of 61 (43%; 95% confidence interval 30% to 56%) for patients who received etomidate. For patients who survived to hospital discharge, the median length of stay was 11.3 days in the midazolam group versus 11.8 days in the etomidate group; for patients who died, the median length of stay was 2.9 days in the midazolam group versus 3.3 days in the etomidate group.

Conclusion: Patients with suspected sepsis and who received a single bolus dose of etomidate for rapid sequence intubation showed no significant increase in hospital length of stay compared with patients who received a single bolus dose of midazolam. [Ann Emerg Med. 2010;56:481-489.]

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INTRODUCTION

Background

Etomidate is widely used as an induction agent before emergency endotracheal intubation primarily because it allows for a rapid, smooth, and hemodynamically stable intubation.[1-3] Concern about the use of etomidate in critically ill patients emerged in the early 1980s, soon after its introduction, when *The Lancet* published letters to the editor describing increased mortality in trauma patients in the ICU who were continuously sedated with etomidate.[4,5] These patients had a greater than 50% increase in mortality compared with patients receiving no etomidate, despite the similarities in their severity of illness. Concern arose that the increase in mortality might be due to the effect of etomidate on suppression of adrenocortical function, which had been reported in animals and in critically ill patients.[6-8] This observation led to a warning being added to the package insert that cautioned against the use of etomidate as a prolonged infusion, citing the "hazards of prolonged suppression of endogenous cortisol and aldosterone production." This warning resulted in a cessation in the use of etomidate for continuous sedation.[9]

Etomidate exerts its effects through reversible and dose-dependent blockade of 11-β-hydroxylase and, to a lesser extent, 17-α-hydroxylase, both of which facilitate the conversion of cholesterol to cortisol. Decreased cortisol and aldosterone levels have been documented in several studies and occur approximately 30 minutes after a single bolus dose of etomidate, with the duration of suppression lasting as long as 24 hours and perhaps even 48 hours.[10-17] Whether this temporary and reversible adrenal suppression is of measurable clinical

Editor's Capsule Summary

What is already known on this topic

Etomidate is commonly used as an induction agent to facilitate emergency intubation. Given that single-dose etomidate can cause measurable adrenal suppression, its use in patients with sepsis is controversial.

What question this study addressed

This randomized clinical trial of 122 patients sought to determine whether the use of etomidate to facilitate emergency intubation in patients with suspected sepsis was associated with a prolonged length of hospital stay compared with the use of midazolam.

What this study adds to our knowledge

In an intention-to-treat analysis, the use of etomidate was not found to be associated with an increased hospital length of stay compared with the use of midazolam.

How this is relevant to clinical practice

These results suggest that the use of etomidate to facilitate intubation in patients with sepsis does not appear to affect important patient-oriented outcomes such as hospital length of stay.

significance is the subject of extensive and often fervent discussion but has yet to be determined.[13,14,18-24]

Importance

Multiple studies have found associations between single doses of etomidate and adverse outcomes, such as increases in mortality, hospital length of stay, ICU length of stay, and duration of mechanical ventilation.[10,12,15,25-28] In only one of these studies, of trauma patients rather than patients with sepsis, were the patients randomized to receive etomidate[12]; in the other studies, use of etomidate was at the discretion of the treating physician, thereby limiting the capacity to derive firm conclusions about its effects.

Goals of This Investigation

Our goal in this study was to determine the effect of a single dose of etomidate on hospital length of stay by comparing length of stay of patients with suspected sepsis who received midazolam to those who received etomidate during rapid sequence intubation in the emergency department (ED).

MATERIALS AND METHODS

Study Design

In this prospective, randomized, double-blind, clinical trial, we compared the hospital length of stay of patients who received etomidate (0.3 mg/kg dose) with the length of stay of patients who received midazolam (0.1 mg/kg dose) intravenously for sedation before rapid sequence intubation. In an earlier prospective observational study in our ED, in which the choice of medication for patients with sepsis requiring emergency intubation was made by the treating physician, of 106 patients during a 9-month period, 70% received etomidate, 21% received midazolam, and 4% received alternatives (ketamine or propofol).[29] For the present study, it was believed that no additional risk to the patients would be incurred by the process of formal randomization and that patient condition and urgency of treatment would not provide time for obtaining consent from patients or surrogates. The study was therefore approved by our institutional review board with a waiver of informed consent and was registered with ClinicalTrials.gov before study initiation.[30] An independent 5-member data and safety monitoring board composed of individuals not affiliated with the study was assembled to perform an interim analysis. Members included representatives from Pharmacy, Nursing, the Performance Improvement Department, the Department of Prehospital Care, and the hospital Ethics Committee. Patients or their legally authorized representatives were notified of enrollment in the study by a formal letter describing the study and giving the investigators' contact information for further questions.

Setting and Selection of Participants

The setting was a large, tertiary care suburban hospital with an average volume of more than 90,000 patients annually. The ED has 50 beds; the hospital, almost 700 beds.

Patients eligible for this study were enrolled from November 2007 until May 2009. Patients were eligible if they were older than 18 years, were intubated in the ED, and had a suspected infectious cause for their illness. The criteria for study exclusion were patients younger than 18 years, pregnancy, cardiopulmonary arrest before arrival in the ED, or a do-not-resuscitate status. Eligible patients were identified by their treating physicians and then randomly assigned to receive either etomidate or midazolam in computer-generated blocks of 10. After randomization, patients were confirmed as having sepsis by the study authors, using the following approach. If patients fulfilled 2 of the 4 criteria for the systemic inflammatory response syndrome (temperature greater than 38°C [100.4°F] or less than 36°C [96.8°F], pulse rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min or $PaCO_2$ less than 32 mm Hg, WBC count greater than 12,000μL or less than 4,000μL, or greater than 10% bands) and the presence of a confirmed infection was clearly identified, patients were considered to have sepsis. A confirmed infection was considered present if body fluid culture results were positive, if diagnostic imaging or a physical examination finding was reported in the chart as being consistent with infection (such as pneumonia on chest radiograph, cellulitis on physical examination, or an infected decubitus ulcer on physical examination), or if there

was a strong suspicion of infection, resulting in administration of antimicrobial agents.

Interventions

Patients received either etomidate (0.3 mg/kg) or midazolam (0.1 mg/kg) intravenously before rapid sequence intubation in a double-blind fashion. The dose of each medication was chosen according to current physician practice and previous study findings.[15] Identical study vials containing either etomidate or midazolam, in volume-equivalent concentrations, were prepared by our pharmacy department and stored in kits that also contained a variety of commonly used paralytic agents. Kits were labeled with numbers that reflected the assignment generated by a randomization sequence generator[31] and placed in our automated medication dispensing cabinet (Omnicell, Inc., Mountain View, CA). The remainder of the patients' care, both in the ED and in the ICU, was directed according to the treating physician.

Methods of Measurement

We created a standardized abstraction instrument with Excel (Microsoft, Redmond, WA) for recording patient data, including age, sex, supplemental steroid use in the ED, use of early goal-directed therapy in the ED, time to first dose of antimicrobial agent, vasopressor use in the ED, blood transfusion requirement in the ED, laboratory values, vital signs, source of infection, and incidence of septic shock. Severity of illness was determined by using the Simplified Acute Physiology II (SAPS II) score and the Sequential Organ Failure Assessment (SOFA) score.[32,33] The SAPS II score is a widely used morbidity and mortality scoring system for medical and surgical ICU patients.[32] The SOFA score, which is a 6-organ dysfunction/failure score that measures multiple organ failure, was created in a consensus meeting of the European Society of Intensive Care Medicine as an indicator of prognosis and illness severity trend in ICU patients.[33] For patients with confirmed sepsis, the severity of illness was also determined by the Mortality in Emergency Department Sepsis score, a prospectively derived and validated clinical prediction rule with scores ranging from 0 to 27, with a score of greater than 15 indicating severe illness with an expected mortality of greater than 50%.[34]

Data Collection and Processing

Data were collected on all randomized patients by one of the study investigators in a blinded fashion. Patients were monitored throughout their hospital stay to determine primary and secondary outcomes.

Outcome Measures

The primary outcome of the study was hospital length of stay. Secondary outcomes included inhospital mortality, ICU length of stay, and length of time intubated. Data on length of stay and length of time intubated were analyzed as continuous outcomes, whereas mortality was analyzed as a dichotomous outcome.

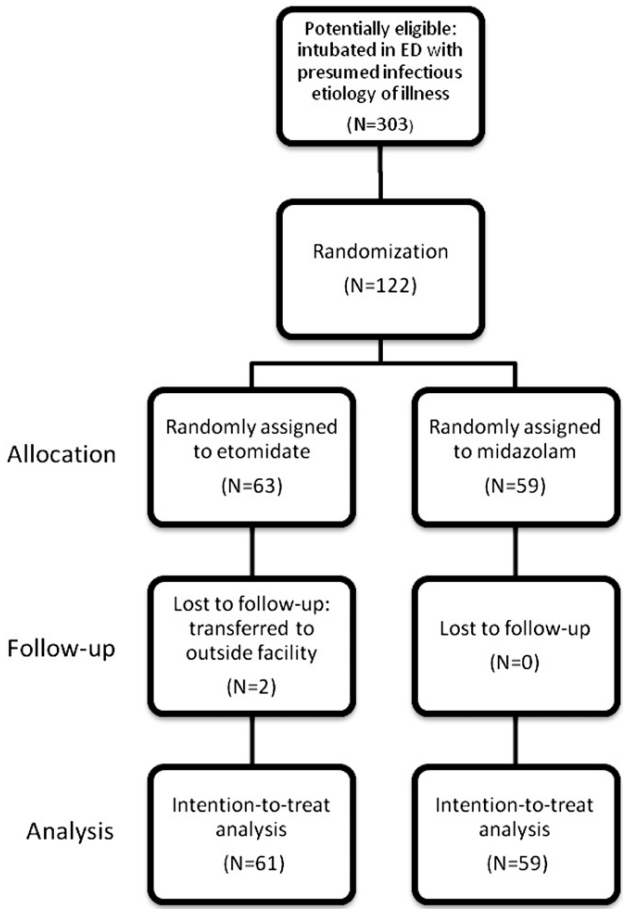

Figure 1. Study flow diagram.

Primary Data Analysis

Sample size was determined for the primary outcome, hospital length of stay, by using existing published data. These data suggested almost a 3-day difference in hospital length of stay for patients with sepsis who receive single-bolus doses of etomidate (12 days for patients who receive etomidate and 9 days for patients who receive alternative agents, with an SD of 5 days and 6 days, respectively).[29] We estimated that 53 patients per group would allow detection of a 3-day difference in hospital length of stay by using parametric assumptions with a 2-sided type I error rate of 5% and a power of 80%.[35] Anticipating that hospital length of stay was likely to be a non-normal variable, we adjusted our estimates upward by 15%, resulting in an estimated sample size requirement of 60 patients per group.

We compared baseline characteristics and primary and secondary clinical outcomes on an intention-to-treat basis according to the randomized study group assignment. Hospital length-of-stay data were compared with the Mann-Whitney U test, and mortality data were compared with the χ^2 test. We compared rates of death with Kaplan-Meier survival curves and log-rank statistics. We considered P values less than .05 to be

Table 1. Demographics and characteristics of the intention-to-treat population.

Characteristic	Midazolam, N=59	Etomidate, N=63	Difference (95% CI for Difference)
Age, y, median (IQR)	73 (60 to 80)	70 (60 to 83)	3 (−5 to 6)
Male, No. (%, 95% CI)	36 (61, 48 to 72)	33 (52, 40 to 64)	9% (−9% to 2%5)
Steroids in ED, No. (%, 95% CI)	28 (48, 35 to 60)	20 (32, 22 to 44)	16% (−2% to 32%)
Steroids within 24 hours, No. (%, 95% CI)	35 (59, 47 to 71)	29 (46, 34 to 58)	13% (−4% to 30%)
SAPS II score, mean (SD)	55 (16)	53 (16)	2 (−4 to 8)
SOFA score, mean (SD)	8 (3)	7 (3)	1 (−0.1 to 2)
Vasopressors in ED, No. (%, 95% CI)	24 (41, 29 to 53)	25 (40, 29 to 52)	1% (−16% to 18%)
Transfusion in ED, No. (%, 95% CI)	5 (9, 4 to 18)	6 (10, 4 to 19)	1% (−10% to 12%)
MAP, mm Hg, median (IQR)	77 (54 to 95)	75 (64 to 97)	2 (−14 to 7)
Pulse rate, beats/min, mean (SD)	110 (30)	110 (25)	0 (−10 to 10)
Lactate, mmol/L, median (IQR)	2.8 (1.7 to 5)	2.5 (1.6 to 3.9)	0.3 (−0.5 to 0.9)
Cortisol, μg/dL, median (IQR)	26 (17 to 55)	24 (20 to 50)	2 (−9.7 to 8)

MAP, Mean arterial pressure.

significant. Statistical analysis was performed with SPSS (version 15.0; SPSS, Inc., Chicago, IL). Our external data and safety monitoring board performed an interim analysis of hospital length of stay and mortality data after half of the patients had been enrolled. A Bonferroni-corrected *P* value of .025 was used as the threshold for statistical significance; a value below this would indicate that the trial should be stopped.

RESULTS

Characteristics of Study Subjects

Figure 1 shows the study flow diagram. Throughout the study period, 303 patients were eligible for enrollment, defined as patients who were intubated in the ED and had a presumed infectious cause for illness. Of these, a total of 122 patients were enrolled; 63 received etomidate and 59 received midazolam (intention-to-treat analysis). The primary reason for not enrolling patients was the lack of an available study investigator, study coordinator, or ED pharmacist to facilitate enrollment of the patient by the treating physician. Patients who were not enrolled were identified through access to the ED Omnicell medication dispenser, which allows queries on the use of all medications used for intubation. Two patients who received etomidate were lost to follow-up after transfer to outside institutions. Baseline characteristics, including the severity of illness of the 122 patients who were enrolled, were similar to those of the 181 patients who were not enrolled. The baseline characteristics of the intention-to-treat population are seen in Table 1.

Main Results

In the intention-to-treat analysis of all randomized patients (summarized on the left side of Table 2), we found that patients receiving midazolam had a median hospital length of stay of 9.5 days (interquartile range [IQR] 4.6 to 16 days) compared with 7.3 days (IQR 3.1 to 13 days) for those receiving etomidate (Figure 2). In our secondary outcome of ICU length of stay, we found no significant difference between patients receiving midazolam and patients receiving etomidate (4.2 days, IQR 2.2 to 6.9 days, versus 3.1 days, IQR 1.9 to 5.6 days). We also found no significant difference in ventilator days between patients who received midazolam and patients who received etomidate (2.8 days, IQR 1.5 to 5.5 days, versus 2.1 days, IQR 1.3 to 4.1 days). Inhospital mortality was 21 of 59 (36%; 95% confidence interval [CI] 24% to 49%) for patients receiving midazolam and was 26 of 61 (43%; 95% CI 30% to 56%) for those receiving etomidate. Kaplan-Meier survival analysis likewise showed no statistically significant differences between groups (*P*=.22) (Figure 3). In a subgroup analysis examining hospital length of stay for patients who survived to hospital discharge compared with patients who died, the median length of stay for patients who survived to hospital discharge was 11.3 days (IQR 8.5 to 17 days) in the midazolam group versus 11.8 days (IQR 6.2 to 14 days) in the etomidate group; for patients who died, the median length of stay was 2.9 days (IQR 1.2 to 11 days) in the midazolam group versus 3.3 days (IQR 1.0 to 9.1 days) in the etomidate group (Figure 4). The decision to use steroid supplementation was left to the treating physicians. The mortality of patients who received midazolam without steroid supplementation within 24 hours was 9 of 24 (38%; 95% CI 21% to 57%) versus 12 of 35 (34%; 95% CI 21% to 51%) for patients who received steroid supplementation. For those who received etomidate without steroid supplementation, the mortality was 13 of 32 (41%; 95% CI 25% to 58%) compared with 13 of 29 (45%; 95% CI 28% to 62%) for those who received steroid supplementation. We did not find a significant effect on mortality when incorporating the use of steroids or the use of early goal-directed therapy into a logistic regression model (odds ratio 0.9, 95% CI 0.31 to 2.8, and odds ratio 0.54, 95% CI 0.24 to 1.2, respectively). Pulse oximetry measurements, as well as systolic blood pressure values, for the patients who received etomidate were similar to those receiving midazolam, both before and after intubation (Table 3). A total of 15 of 59 (25%; 95% CI 16% to 38%) patients in the midazolam group and 16 of 63 (25%; 95% CI 16% to 37%) in

Table 2. Primary and secondary outcomes of the intention-to-treat and per-protocol populations.*

Outcome	Intention-to-Treat Population				Per-Protocol Population			
	Midazolam, N=59	Etomidate, N=61	Difference (95% CI for Difference)	*P* Value	Midazolam, N=51	Etomidate, N=45	Difference (95% CI for Difference)	*P* Value
Primary outcome								
Hospital LOS, days	9.5 (4.6 to 15.7)	7.3 (3.1 to 12.9)	2.2 (−0.7 to 4.8)	.17	10.2 (6.7 to 18)	9.2 (4.5 to 12.9)	1.0 (−0.1 to 5.9)	.06
Secondary outcomes								
ICU LOS, days	4.2 (2.2 to 6.9)	3.1 (1.9 to 5.6)	1.1 (−0.3 to 1.8)		4.2 (2.6 to 6.8)	3.4 (2.2 to 5.7)	0.8 (−0.5 to 1.8)	
Ventilator days	2.8 (1.5 to 5.5)	2.1 (1.3 to 4.1)	0.7 (−0.3 to 1.5)		2.8 (1.6 to 5.3)	2.3 (1.5 to 4.4)	0.5 (−0.5 to 1.4)	
Inhospital mortality, No. (%, 95% CI)	21 (36, 24 to 49)	26 (43, 30 to 56)	7% (−10% to 24%)		17 (33, 21 to 48)	19 (42, 28 to 58)	9% (−10% to 27%)	

LOS, Length of stay.
*Numbers are medians and IQRs unless otherwise indicated.

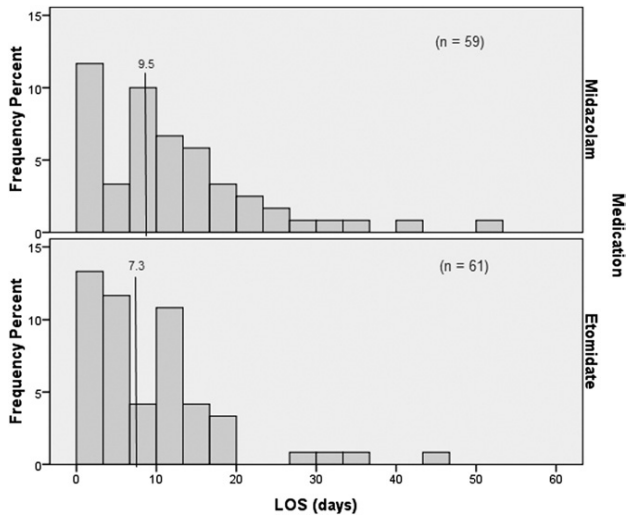

Figure 2. Histogram of hospital length of stay (LOS) for all patients, including surviving patients and patients who died. Vertical indicator lines show medians for each group. Means were 9.6 days for the etomidate group and 12 days for the midazolam group.

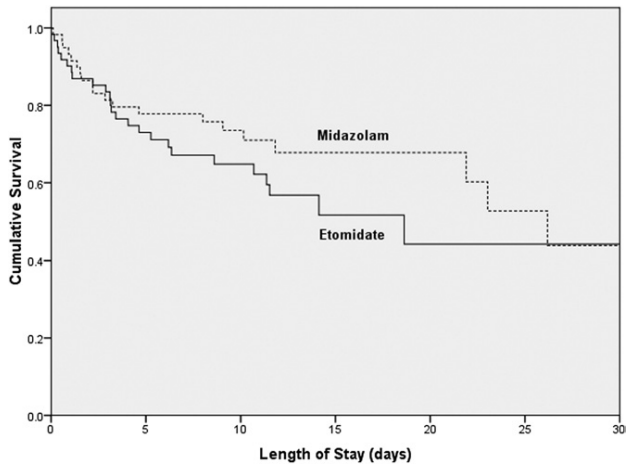

Figure 3. Kaplan-Meier survival curve.

the etomidate group developed a systolic blood pressure less than 90 mm Hg after intubation.

Given the urgency surrounding the patient in need of rapid sequence intubation, the treating physician was unable to determine with 100% certainty at enrollment whether a patient had a sepsis syndrome. A number of patients initially thought to have sepsis were subsequently found to have alternative causes for their critical illness requiring intubation. Therefore, we also performed a secondary per-protocol analysis of patients with confirmed sepsis, established after enrollment. We determined that 96 of the 122 patients met these criteria. Of these patients, 45 received etomidate and 51 received midazolam. Baseline characteristics of this per-protocol population are seen in Table 4. A small number of patients were found to have more than

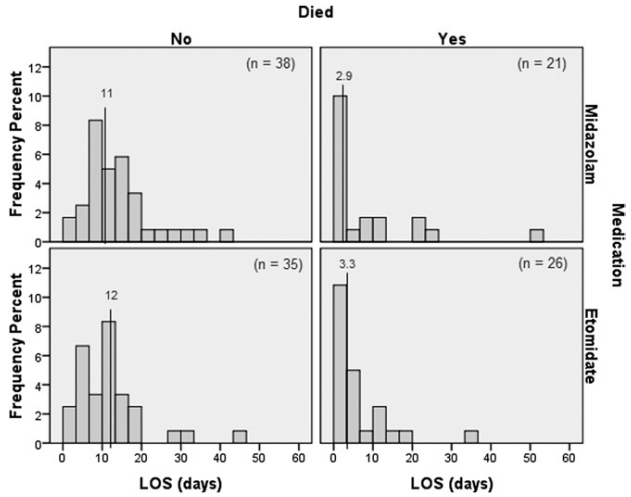

Figure 4. Histogram of hospital length of stay (LOS) for surviving patients (left 2 panels) and patients who died (right 2 panels). Vertical indicator lines show medians for each group. Means for those who died were 6.1 days for the etomidate group and 8.9 days for the midazolam group and for those who survived the means were 12.1 days for the etomidate group and 14 days for the midazolam group.

one source of sepsis (listed under the category "Lower Respiratory Infection and Other"). The causes of illness for patients without confirmed sepsis (with number of patients in parentheses) included intracranial hemorrhage (5), congestive heart failure or myocardial infarction (4), seizure (3), toxic ingestion (3), chronic obstructive pulmonary disease (2), gastrointestinal bleeding (2), trauma (2), pulmonary embolism (1), pneumothorax (1), diabetic ketoacidosis (1), and undetermined (2).

In the per-protocol analysis (summarized on the right side of Table 2), we found a median hospital length of stay of 10.2 days (IQR 6.7 to 18 days) in the midazolam group and 9.2 days (IQR 4.5 to 13 days) in the etomidate group. In a subgroup analysis of the patients with confirmed sepsis who survived to hospital discharge, no significant difference in hospital length of stay was observed for patients receiving midazolam compared with etomidate (12 days, IQR 6.2 to 14 days, versus 11 days, IQR 8.5 to 17 days). In our secondary outcome of ICU length of stay, we found no significant difference between patients receiving midazolam and patients receiving etomidate in the per-protocol analysis (4.2 days, IQR 2.6 to 6.8 days, versus 3.4 days, IQR 2.2 to 5.7 days). We also found no significant difference in ventilator days between patients who received midazolam and patients who received etomidate in the per-protocol analysis (2.8 days, IQR 1.6 to 5.3 days, versus 2.3 days, IQR 1.5 to 4.4 days). In the per-protocol analysis we found an inhospital mortality of 17 of 51 (33%; 95% CI 21% to 48%) for patients who received midazolam and 19 of 45 (42%; 95% CI 28% to 58%) for those who received etomidate. In the per-protocol patients, the mortality for patients who received midazolam without steroid supplementation within 24 hours was 5 of 17 (29%; 95% CI 13% to 53%) versus 12 of 34 (35%; 95% CI 21% to 52%) for those who received steroid supplementation. For patients who received etomidate without steroid supplementation, the mortality was 7 of 20 (35%; 95% CI 18% to 57%), whereas it was 12 of 25 (48%; 95% CI 30% to 67%) for those who received steroid supplementation.

LIMITATIONS

Because of limitations in the availability of study investigators and pharmacists, we were unable to enroll all potentially eligible patients, raising the possibility that our study sample was not representative of our entire patient population. Enrolled patients were nevertheless similar to patients not enrolled. The use of additional adjunctive therapies such as activated protein C, tight glucose control, and low-tidal-volume ventilation may also have varied between groups and was not factored into our analysis. We did not monitor subsequent uses of etomidate during patients' hospitalizations, which could further contribute to confounding.

We chose hospital length of stay as the primary outcome to perform a meaningful study within the constraints of our facility and resources; however, more direct outcome measures, such as mortality, may be more appropriate as a primary outcome of interest for future studies. Although we focused on objective measures of outcome, we did not use multiple observers or measure agreement between observers and recorders of data points.

Our study, although sufficiently powered according to our primary outcome, was nevertheless underpowered to detect potentially important differences in mortality. According to our results and the mortality we observed, the size of our study sample would have allowed detection of a mortality difference of 25% between patients who received etomidate and patients who received midazolam. Moreover, a noninferiority design may be a more appropriate method of identifying this difference, in which case a further increase in sample size may be required.

DISCUSSION

Etomidate is an ideal agent for use in the patient with sepsis because of its predictability in dosing, reliable hypnotic effect, rapid onset, and short duration of effects and because it has no effect on histamine release, which contributes to its hemodynamic stability.[2] However, many previous studies have suggested adverse outcomes from the use of single-bolus etomidate in patients with sepsis, including an absolute increase in mortality ranging from 15% to almost 40%,[13,25,26] and trends toward increased hospital and ICU length of stay in surviving patients who receive etomidate.[12,29] We found no significant differences in the primary outcome of hospital length of stay between patients who received etomidate and those who received midazolam. Furthermore, we did not detect a difference between groups in any of our secondary outcomes,

Table 3. Preintubation and postintubation parameters.

Parameter, Median (IQR)	Midazolam, N=59	Etomidate, N=63	Difference (95% CI for Difference)
Pulse oximetry, preintubation, %	99 (95 to 100)	99 (95 to 100)	0 (−1 to 0)
Pulse oximetry, postintubation, %	100 (99 to 100)	100 (100 to 100)	0 (0 to 0)
SBP, preintubation, mm Hg	122 (97 to 147)	119 (92 to 147)	3 (−14 to 15)
SBP, postintubation, mm Hg	106 (89 to 148)	112 (92 to 148)	6 (−13 to 16)

SBP, Systolic blood pressure.

Table 4. Demographics and characteristics of the per-protocol population.

Characteristic	Midazolam, N=51	Etomidate, N=45	Difference (95% CI for Difference)
Demographic factors			
Age, y, mean (SD)	70 (15)	72 (13)	2 (−4 to 8)
Male, No. (%, 95% CI)	31 (61, 47 to 73)	24 (53, 39 to 67)	8% (−12% to 26%)
Severity of illness			
MEDS score, mean (SD)	11 (5)	13 (4)	2 (0.2 to 4)
SAPS II score, mean (SD)	56 (16)	56 (14)	0 (−6 to 6)
SOFA score, mean (SD)	8 (3)	8 (3)	0 (−1 to 1)
Septic shock, No. (%, 95% CI)	23 (45, 32 to 59)	28 (62, 48 to 75)	17% (−3% to 35%)
Treatment factors			
Steroids in ED, No. (%, 95% CI)	27 (53, 40 to 66)	17 (38, 25 to 52)	15% (−5% to 33%)
Steroids within 24 hours, No. (%, 95% CI)	34 (67, 53 to 78)	25 (56, 41 to 69)	11% (−8% to 29%)
Vasopressors in ED, No. (%, 95% CI)	22 (43, 31 to 57)	24 (53, 39 to 67)	10% (−10% to 29%)
Transfusion in ED, No. (%, 95% CI)	3 (6, 2 to 16)	3 (7, 2 to 18)	1% (−10% to 13%)
EGDT in ED, No. (%, 95% CI)	25 (49, 36 to 62)	29 (64, 50 to 77)	15% (−4% to 34%)
Hours to antibiotics, median (IQR)	2.5 (1.5 to 3.8)	2.8 (2.0 to 4.1)	0.3 (−0.4 to 0.9)
Physiologic variables			
MAP, mm Hg, mean (SD)	76 (26)	74 (23)	2 (−8 to 12)
Pulse rate, beats/min, mean (SD)	112 (28)	108 (26)	4 (−7 to 15)
Laboratory findings			
Lactate, mmol/L, median (IQR)	2.8 (1.7 to 4.1)	2.6 (1.7 to 4.1)	0.2 (−0.7 to 0.9)
Cortisol, mcg/dL, median (IQR)	26 (17 to 55)	25 (20 to 50)	1 (−11 to 7)
Source of sepsis			
Lower respiratory infection, No. (%, 95% CI)	25 (49, 36 to 62)	20 (44, 31 to 59)	5% (−15% to 24%)
Lower respiratory infection and other, No. (%, 95% CI)	6 (12, 6 to 23)	9 (20, 11 to 34)	8% (−7% to 23%)
Urinary tract infection, No. (%, 95% CI)	7 (14, 7 to 26)	6 (13, 6 to 26)	1% (−14% to 14%)
Bacteremia, No. (%, 95% CI)	2 (4, 1 to 13)	3 (7, 2 to 18)	3% (−8% to 14%)
Intra-abdominal infection, No. (%, 95% CI)	1 (2, 0.4 to 10)	2 (4, 1 to 15)	2% (−7% to 13%)
Integumentary infection, No. (%, 95% CI)	1 (2, 0.4 to 10)	1 (2, 0.4 to 12)	0% (−8% to 10%)
Joint space infection, No. (%, 95% CI)	1 (2, 0.4 to 10)	0 (0, 0 to 8)	2% (−6% to 10%)
Undetermined, No. (%, 95% CI)	8 (16, 8 to 28)	4 (9, 4 to 21)	7% (−7% to 20%)

MEDS, Mortality in Emergency Department Sepsis; *EGDT*, early goal-directed therapy.

including ICU length of stay, ventilator days, or mortality. Of note, in our study population, we had proportionally more deaths of patients who received etomidate, which had the potential to affect our primary endpoint of hospital length of stay, making it appear that patients who received etomidate had a shorter hospital length of stay. Therefore, we performed a subgroup analysis comparing hospital length of stay for patients who survived to hospital discharge and still found no significant difference between patients who received midazolam and those who received etomidate.

To our knowledge, our study is the only randomized, double-blind comparison of the effects of using either etomidate or an alternative agent for intubation of patients with presumed sepsis. Schenerts et al,[15] in 2001, randomized 31 patients to receive either etomidate or midazolam and found increased adrenocortical dysfunction in patients who received etomidate.[15] That study was limited, however, by a lack of blinding of the treating physicians to their group assignment and by the enrollment of a heterogeneous patient population with uncertain causes of illness.[15] In 2008, Hildreth et al[12] compared the effects of etomidate with a combination of fentanyl and midazolam in 30 adult trauma patients. The etomidate group was found to have significantly lower cortisol levels and increased hospital length of stay, ICU length of stay, and ventilator days compared with those of the patients receiving fentanyl and midazolam, but the investigators, likewise, were not blinded, and additional limitations posed potential threats to external validity (including a large number

of excluded patients, undetermined reasons for exclusion, and small overall study size).[12] Shortly before completion of our study, Jabre et al[36] reported the results of a randomized trial comparing etomidate with ketamine in a heterogeneous population of 469 patients and found no difference in any primary or secondary endpoints; however, their study was incompletely blinded (enrolling physicians were aware of the study group assignment) and included a total of only 76 patients with sepsis.

Our current analysis of 122 patients in total, 96 of whom were diagnosed with sepsis, overcomes many of the limitations of previous observational studies and raises the possibility that previous findings were influenced by confounding variables. Nevertheless, the relatively small size of our study, combined with the point estimates of mortality showing a 7% increase in all patients who received etomidate and a 9% increase in patients who had sepsis and received etomidate, raises the possibility that our investigation was underpowered to detect statistical significance in what may be a clinically important difference in mortality. Jabre et al,[36] in a subgroup analysis of patients with sepsis from their recent study, similarly found a nonstatistically significant mortality difference of 8% (42% in the etomidate group and 34% in the ketamine group). Detecting a 1-sided, statistically significant mortality difference of this size would require at least 360 patients per group, which would entail a significantly longer study period or the enlistment of multiple study sites.

Overall, we did not find significant effects from the use of steroid supplementation in our patients, although trends toward increased mortality were evident with supplemental steroid use, irrespective of induction agent. Because our study was not designed to obtain quantitative measures of adrenal function, we did not direct the subsequent care of patients after randomization, nor did we require physicians to obtain cortisol levels or to use steroids in their patients. Throughout the course of our study, our institution generally reserved the use of corticosteroids for patients who remained hypotensive despite treatment with vasopressors. Consequently, any trends toward increased mortality observed with the use of steroids are likely to be confounded by the increased illness severity of patients who receive steroids.

In conclusion, for patients who had suspected sepsis and were intubated in the ED, we found no significant difference in hospital length of stay between patients who received etomidate as an induction agent and those who received midazolam.

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Address for correspondence: Karis L. Tekwani, MD, Advocate Christ Medical Center, Department of Emergency Medicine, 4440 W 95th St, Oak Lawn, IL 60453; 708-684-4077, fax 708-684-1028; E-mail karis711@hotmail.com.

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