Single-Dose Etomidate Is Not Associated With Increased Mortality in ICU Patients With Sepsis: Analysis of a Large Electronic ICU Database*

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Objective: Retrospective analyses of several trials suggest etomidate may be unsafe for intubation in patients with sepsis. We evaluated the association of etomidate and mortality in a large cohort of septic patients to determine if single-dose etomidate was associated with increased in-hospital mortality.

Design and Setting: Retrospective cohort study at the Philips *e*ICU Research Institute ICU clinical database.

Interventions: None.

Patients: Among 741,036 patients monitored from 2008 through 2010, we identified 2,014 adults intubated in the ICU 4–96 hrs after admission, having clinical criteria consistent with sepsis, severe sepsis, or septic shock. In all, 1,102 patients received etomidate and 912 received other induction agents for intubation.

Measurements and Main Results: The primary endpoint was in-hospital mortality, but we also evaluated demographic and clinical factors, severity of illness, ICU mortality, ICU length of stay, hospital length of stay, ventilator days, and vasopressor days. Competing risk Cox proportional hazard regression models were used for primary outcomes. Demographics and illness severity were similar between the groups. Hospital mortality was similar between the groups (37.2% vs. 37.8%, $p = 0.77$), as were ICU mortality (30.1% vs. 30.2%, $p = 0.99$), ICU length of stay (8.7 days vs. 8.9 days, $p = 0.66$), and hospital length of stay (15.2 vs. 14.6 days, $p = 0.31$). More patients in the etomidate group received steroids before and after intubation (52.9% vs. 44.5%, $p < 0.001$), but vasopressor use and duration of mechanical ventilation were similar. No regression model showed an independent association of etomidate with mortality, shock, duration of mechanical ventilation, ICU or hospital length of stay, or vasopressor use. A hospital mortality model limited to only patients with septic shock ($n = 650$) also showed no association of etomidate and hospital mortality.

Conclusion: In a mixed-diagnosis group of critically ill patients with sepsis, severe sepsis, and septic shock, single-dose etomidate administration for intubation in the ICU was not associated with higher mortality or other adverse clinical outcomes. (*Crit Care Med* 2013; 41:774–783)

Key Words: etomidate; induction; intubation; mortality; sepsis; shock

***See also p. 917.**

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Etomidate is one of the most commonly used induction agents for intubation in emergency departments in the United States (1) because of its purported rapid onset of sedation, amnestic properties, short duration of action, limited hemodynamic effects, and tendency to create adequate intubating conditions (2, 3). Unfortunately, etomidate also has an inhibitory effect on adrenal function (4–11). It inhibits 11-β-hydroxylase, which converts 11-deoxycortisol to cortisol. This reversible inhibition has been reported to last up to 72 hrs and to reduce steroidogenesis in patients after infusion or bolus administration (5, 8, 9, 11). Transient adrenocortical suppression has been demonstrated after single-dose etomidate in healthy patients undergoing elective surgery (12) and in patients after trauma, whereas prolonged infusions of etomidate are associated with higher mortality after prolonged infusion in critically ill patients (13). The use of single-dose etomidate

in sepsis or septic shock has also been shown to cause chemical evidence of adrenal insufficiency, but the clinical consequences of this are unclear (5, 7–9, 12, 14).

Small subgroup analyses from two prominent randomized controlled trials suggest higher mortality in septic patients intubated with etomidate (5, 7, 8), but corticosteroid replacement after etomidate does not seem to affect mortality (10, 15). It is unclear if these patients were sicker than the patients intubated with other agents, or if etomidate itself was to blame for the increased mortality. Etomidate use in patients with sepsis, who are often hypotensive and might benefit most from its administration, is therefore controversial, and further investigation has been suggested (6, 16–18). Recent editorials have cautioned clinicians about etomidate (16, 18); one stated "until the safety of etomidate is demonstrated in patients with severe sepsis and septic shock, this drug is best avoided for emergent intubations" (18).

Based on these serious concerns, the broad utilization and effectiveness of etomidate as an intubating agent, and an anticipated delay of years before the safety of etomidate may be tested prospectively, we determined to evaluate its safety retrospectively. Our investigation was intended to determine if the use of single-dose etomidate for intubation was associated with higher in-hospital mortality or other clinically important endpoints in a large cohort of ICU patients with sepsis, severe sepsis, or septic shock.

MATERIALS AND METHODS

The Philips *e*ICU Research Institute (*e*RI) database comprises an extensive dataset of critically ill adult patients remotely monitored in tele-ICUs around the United States (19, 20). After identifying all ICU admissions, we then identified adults intubated in the ICU. Patients were excluded if they were younger than 18 yr, had incomplete medication or clinical records, were intubated outside the ICU, had previously received etomidate, or had evidence of multiple intubations (**Fig. 1**). Intubation in the ICU was required to ensure that baseline physiology and medications were accurately captured relative to the timing of the intubation. Patients meeting these initial criteria were then separated into those with sepsis at the time of intubation and those without. The *e*RI database includes extensive medical history and demographics, physical examination findings, diagnoses, laboratory data, medications, demographics, and vital signs, which are either documented directly or imported through electronic Health Level 7 International standard interfaces into the electronic medical record.

Data collected from clinical flow sheets included average mean arterial pressure during 24 hrs before and after intubation, lowest systolic blood pressure 24 hrs before and after intubation, and average heart rate 24 hrs before and after intubation. Induction medications for intubation were recorded. Vasopressor use was defined as the number of 24-hr days following intubation during which a patient received epinephrine, norepinephrine, phenylephrine, dopamine, dobutamine, and/or vasopressin. Administration of mineralocorticoids and glucocorticoids in the 24 hrs before intubation and during the 72 hrs after intubation was independently evaluated.

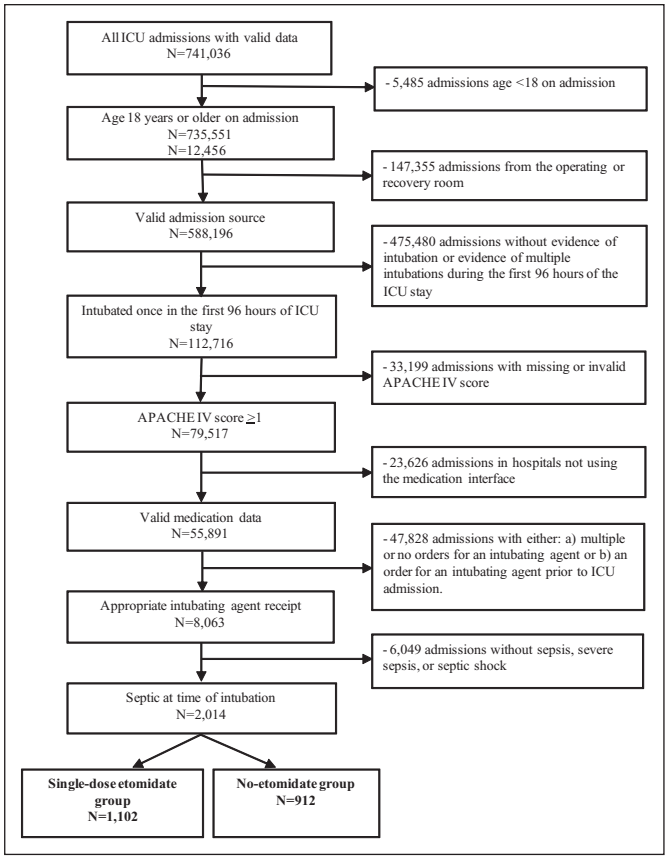

Figure 1. Patient selection flow diagram. APACHE = Acute Physiology and Chronic Health Evaluation.

Septic patients were defined in any one of three ways:

1. A suspected or confirmed infection plus two or more of the following criteria within 24 hrs of intubation: Temperature more than 38°C or less than 36°C, heart rate more than 90 beats/min, hyperventilation with respiratory rate more than 20/min or $Paco_2$ less than 32 mm Hg, or white blood cell count more than 12,000 cells/μL or less than 4,000 μL; or
2. Patients described as having sepsis, severe sepsis, or septic shock as "active problems/diagnoses" in the electronic medical record within 24 hrs of the onset of mechanical ventilation; or
3. Patients with an admission diagnosis of sepsis.

To verify that induction medications were not being missed, we excluded patients intubated in the operating room, the emergency department, and otherwise outside of the primary treating ICU. An ICU intubation was defined as a patient transitioning from unventilated to ventilated status, and the medication administration interface showing the administration of a single-dose neuromuscular blockade agent and/or etomidate. Although this methodology excluded patients intubated without either etomidate or neuromuscular blockade, it was determined to be the most reliable method of verifying the intubation occurred in the controlled setting of the ICU, where all physiology and medication usage was accounted. The exposure of interest was not the intubation event, but use of

etomidate compared with no etomidate during induction for intubation. The primary endpoint was in-hospital mortality in septic patients. Secondary endpoints included ICU mortality, hospital and ICU length of stay (LOS), days of mechanical ventilation, and days of vasopressor use in a priori identified subgroups of these septic patients: those with severe sepsis and those with septic shock. Specific patient characteristics include age, gender, admission Acute Physiology and Chronic Health Evaluation (APACHE) IV score (Cerner, Kansas City, MO), predicted mortality (based on APACHE IV predictions), comorbid conditions at time of admission (defined as "chronic health conditions" and "immunosuppression" in the APACHE IV scoring system), and etiology of the infection, if available.

Our sample size was guided by retrospective subgroup analyses of the Ketamine Versus Etomidate During Rapid Sequence Intubation: Consequences on Hospital Morbidity (KETASED) (7) and Corticosteroid Therapy of Septic Shock Study (CORTICUS) (5) trials. Both trials identified possible harm from etomidate administration in septic patients. The weaker association was seen in KETASED; in that trial, septic patients intubated with etomidate had a 28-day mortality rate of 41% vs. 34% among those intubated with ketamine. Based on this difference, we calculated that 778 patients in each arm would be needed to detect a statistically significant mortality (total sample size 1556), at a two-tailed α value of 0.05, and 80% power. Because of the potential for misclassification inherent to retrospectively gathered data, we added 20% to the power calculation to account for a 10% misclassification of patients, bringing to 934 the number of patients required in each arm. We then went chronologically backward through the *e*RI database using our search strategy (see Fig. 1) until we were comfortable that an adequate sample size existed to answer the research question.

Baseline characteristics of patients who received etomidate for intubation were compared with those who did not, using chi-square or Fisher's exact tests for categorical variables and *t* tests or their nonparametric equivalent for continuous variables. To quantify the association between etomidate exposure and each outcome (except vasopressor days), a competing risk analysis was performed using the Fine and Gray method (21). A competing risk analysis is useful because the traditional survival models impose an unreasonable assumption that survivors who are censored are similar to their peers who experience the event. For mortality models, the primary event of interest was in-hospital (or ICU) mortality, and the competing event was discharge from the hospital (or ICU) alive. For LOS and ventilator-day models, the events of interest were time to being discharged alive and unassisted breathing, respectively, with the competing event being death. The subhazard ratio for each covariate with the corresponding event of interest is reported. An interaction between etomidate exposure and time was added to the models to test the assumption of proportional hazards over time. Negative binomial regression was used to model the association between etomidate use and vasopressor days. Finally, the regression model for in-hospital mortality was repeated with inclusion of only patients with septic shock. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC) and STATA 11 (StataCorp). 2009. Stata Statistical Software: Release 11 (StataCorp LP, College Station, TX) for the competing risk analyses.

TABLE 1. Clinical Characteristics of the Study Cohort, Stratified by Etomidate Use for Intubation

Characteristic	All Septic Patients (*n* = 2014)	Etomidate (*n* = 1102)	No Etomidate (*n* = 912)	*p*
General characteristics				
Age (mean, SD)	60.9 (16.5)	62.5 (15.7)	58.9 (17.2)	< 0.01
Female gender, *n* (%)	944 (46.9)	516 (46.8)	428 (46.9)	0.96
Caucasian, *n* (%)	1570 (78.0)	875 (79.4)	695 (76.2)	0.12
Clinical characteristics				
Admission source, *n* (%)				< 0.01
Emergency room	997 (49.5)	546 (49.5)	451 (49.5)	
Within same hospital	788 (39.1)	456 (41.4)	332 (36.4)	
Direct admit	134 (6.7)	64 (5.8)	70 (7.7)	
Other hospital	95 (4.7)	36 (3.3)	59 (6.5)	
Body mass index (mean, SD)	29.6 (13.0)	29.2 (12.9)	30.2 (13.0)	0.09
APACHE IV score (mean, SD)	84.8 (31.1)	85.4 (30.4)	84.1 (32.0)	0.35
Acute physiology score (mean, SD)	73.0 (29.7)	73.0 (29.4)	73.0 (30.0)	0.99

(*Continued*)

TABLE 1. (*Continued*) Clinical Characteristics of the Study Cohort, Stratified by Etomidate Use for Intubation

Characteristic	All Septic Patients (*n* = 2014)	Etomidate (*n* = 1102)	No Etomidate (*n* = 912)	*p*
APACHE admission diagnosis, *n* (%)				
Sepsis-type (see Appendix 1)	883 (43.8)	479 (43.5)	404 (44.3)	0.71
Received care in a teaching hospital, *n* (%)	542 (26.9)	388 (35.2)	154 (16.9)	< 0.001
Number of hospital beds, *n* (%)				< 0.001
<100	102 (5.1)	55 (5)	47 (5.2)	
100–<250	440 (21.9)	223 (20.2)	217 (23.8)	
250–<500	517 (25.7)	246 (22.3)	271 (29.7)	
> 500	955 (47.4)	578 (52.5)	377 (41.3)	
Received care in a teaching hospital, *n* (%)	542 (26.9)	388 (35.2)	154 (16.9)	< 0.001
Comorbid conditions at admission, *n* (%)				
AIDS	16 (0.8)	6 (0.5)	10 (1.1)	0.17
Hepatic failure	71 (3.5)	41 (3.7)	30 (3.3)	0.60
Lymphoma	23 (1.1)	8 (0.7)	15 (1.6)	0.05
Metastatic cancer	65 (3.2)	36 (3.3)	29 (3.2)	0.91
Leukemia	51 (2.5)	28 (2.5)	23 (2.5)	0.98
Immunosuppression	112 (5.6)	66 (6.0)	46 (5.0)	0.36
Cirrhosis	58 (2.9)	29 (2.6)	29 (3.2)	0.46
Myocardial infarction within past 6 mos	16 (0.8)	7 (0.6)	9 (1.0)	0.38
Diabetes	454 (22.5)	254 (23.0)	200 (21.9)	0.55
Received noninvasive ventilation within 24 hrs before initial intubation, *n* (%)	300 (14.9)	156 (14.2)	144 (15.8)	0.31
Mean arterial pressure in mm Hg in 1 hr before intuba tion (mean, SD)	77.5 (18.4)	76.2 (17.6)	79.1 (19.2)	< 0.01
Any steroid within 24 hrs before intubation, *n* (%)	496 (24.6)	295 (26.8)	201 (22.0)	0.01
Any vasopressor within 24 hrs before intubation, *n* (%)[a]	319 (32.6)	192 (32.5)	127 (32.6)	0.97
APACHE predicted ICU mortality				
Mean, SD	0.236 (0.291)	0.233 (0.294)	0.240 (0.288)	0.98
Median, IQR	0.170 (0.065–0.379)	0.172 (0.067–0.373)	0.163 (0.065–0.387)	0.64
APACHE predicted hospital mortality				
Mean, SD	0.269 (0.419)	0.265 (0.433)	0.276 (0.401)	0.21
Median, IQR	0.260 (0.111–0.520)	0.267 (0.118–0.525)	0.246 (0.105–0.509)	0.32

APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range.

[a]Vasopressor use was assessed by continuous infusion administration records available in only 979 of the 2,014 patients.

RESULTS

In all, 8,063 of the 741,036 patients monitored from 2008 through the third quarter of 2010 satisfied study criteria (see Fig. 1). These were then separated into 2014 with sepsis at the time of intubation and 6049 without. Characteristics of the septic patients are described in **Table 1**. Patients who received etomidate were older than those not receiving etomidate, had lower preintubation blood pressure, were more likely to have received steroids before intubation, and were more likely to have been treated in an academic medical center. They were

also slightly less likely to have been transferred from other hospitals. In other respects, including vasopressor use and APACHE IV-predicted mortality, the groups were similar. Based on the APACHE IV predictions (22), the mean predicted hospital mortality for the overall septic cohort was 40% and corresponded well with the actual mortality of 38%.

Patients receiving etomidate for intubation also frequently (64.5%) received neuromuscular blockade for intubation. By definition, all patients in the nonetomidate group received a neuromuscular blocking agent. Patients who received etomidate for intubation less often received propofol for sedation after intubation (37.8% vs. 42%, $p < 0.01$). Patients

TABLE 2. Medication Use Stratified by Etomidate Exposure

Medication Use	All Septic Patients ($n = 2014$), n (%)	Etomidate ($n = 1102$), n, (%)	No Etomidate ($n = 912$), n (%)	p
Intubating agents				
Any single-dose neuromuscular blocker	1623 (80.6)	711 (64.5)	912 (100.0)	< 0.01
Succinylcholine	905 (44.9)	467 (42.4)	438 (48.0)	0.01
Pancuronium	76 (3.8)	19 (1.7)	57 (6.3)	< 0.01
Vecuronium	697 (34.6)	270 (24.5)	427 (46.8)	< 0.01
Rocuronium	253 (12.6)	110 (10.0)	143 (15.7)	< 0.01
Other sedative use[a]				
Sedative use, 24 to 72 hrs after intubation	765 (78.1)	451 (76.4)	314 (80.7)	0.11
Propofol	411 (42.0)	223 (37.8)	188 (48.3)	< 0.01
Dexmedetomidine	34 (3.5)	24 (4.1)	10 (2.6)	0.21
Midazolam	415 (42.4)	283 (48.0)	132 (33.9)	< 0.01
Lorazepam	94 (9.6)	25 (4.2)	69 (17.7)	< 0.01
Sedative within 24 hrs before intubation	224 (22.9)	124 (21.0)	100 (25.7)	0.09
Sedative use within 72 hrs after intubation	764 (78.0)	451 (76.4)	313(80.5)	0.14
Steroid use				
Any steroid within 24 hrs before intubation	496 (24.6)	295 (26.8)	201 (22.0)	0.01
Dexamethasone or hydrocortisone	176 (8.7)	119 (10.8)	57 (6.3)	< 0.01
Methylprednisolone, prednisolone, or prednisone	338 (16.8)	184 (16.7)	154 (16.9)	0.91
Fludrocortisone	11 (0.5)	9 (0.8)	2 (0.2)	0.13
Any steroid within 72 hrs after intubation	968 (48.1)	571 (51.8)	397 (43.5)	< 0.01
Dexamethasone or hydrocortisone	537 (26.7)	344 (31.2)	193 (21.2)	< 0.01
Methylprednisolone, prednisolone, or prednisone	509 (25.3)	270 (24.5)	239 (26.2)	0.38
Fludrocortisone	31 (1.5)	25 (2.3)	6 (0.7)	< 0.01
Vasopressor use[a]				
Any vasopressor within 24 hrs before intubation	319 (32.6)	192 (32.5)	127 (32.6)	0.97
Any vasopressor within 72 hrs after intubation	676 (69.1)	409 (69.3)	267 (68.6)	0.82
Dopamine	104 (10.6)	60 (10.2)	44 (11.3)	0.57
Dobutamine	67 (6.8)	43 (7.3)	24 (6.2)	0.50
Epinephrine	22 (2.2)	8 (1.4)	14 (3.6)	0.02
Norepinhephrine	602 (61.5)	371 (62.9)	231 (59.4)	0.27
Phenylephrine	145 (14.8)	81 (13.7)	64 (16.5)	0.24
Vasopressin	225 (23.0)	132 (22.4)	93 (23.9)	0.58

[a]Other sedating medications and vasopressor use was assessed by continuous infusion administration records was available in 979 of the 2,014 patients.

TABLE 3. Unadjusted Outcomes

Characteristic	All Septic Patients (*n* = 2014)	Etomidate (*n* = 1102)	No Etomidate (*n* = 912)	*p*
Hospital mortality, *n* (%)	755 (37.5)	410 (37.2)	345 (37.8)	0.77
ICU mortality, *n* (%)	607 (30.1)	332 (30.1)	275 (30.2)	0.99
Hospital LOS, median (IQR)	12.2 (6.3–20.0)	12.7(6.8–20.2)	11.9 (6.0–19.5)	0.13
ICU LOS, median (IQR)	6.4 (3.2–11.5)	6.4 (3.2–11.2)	6.5 (3.0–11.9)	0.88
Ventilator days, median (IQR)	4.1 (1.7–8.4)	4.1 (1.8–8.0)	4.1 (1.5–8.8)	0.82
Postintubation vasopressor days,[a] median (IQR)	2 (0–3)	2 (0–3)	2 (0–3)	0.61

LOS = length of stay; IQR = interquartile range.

[a]Postintubation vasopressor days were defined as the count of 24-hr periods after intubation through the ICU LOS with any evidence of vasopressor use. Additionally, this measure only includes patients who are in ICUs with complete infusion drug information.

who received etomidate more often received steroids both before (26.8% vs. 24.6%, $p = 0.01$) and after intubation (51.8% vs. 48.1%, $p < 0.01$). There was no difference in vasopressor use before or after intubation (**Table 2**).

Unadjusted outcomes are presented in **Table 3**. There was no difference in in-hospital mortality or in any of the secondary outcomes of concern, including vasopressor use, duration of mechanical ventilation, ICU LOS, or hospital LOS. Regression models were then constructed for the primary endpoint (hospital mortality, **Table 4**) and for each secondary outcome of interest.

In the regression model for in-hospital mortality, higher risk of death was associated with increasing age and APACHE IV scores, race, steroid use, and certain comorbid diagnoses. There was no statistical association or any visible trend between etomidate use and mortality. The test for an interaction with time indicated the proportional hazards assumption was not violated in any of the models ($p > 0.05$). Similar regression models were then constructed for each secondary outcome, including vasopressor use, duration of mechanical ventilation, and ICU LOS. In each model, there was no association between etomidate use and the outcome of interest, nor was a nonsignificant trend noted. Finally, the regression model was constructed for in-hospital mortality, including only the 650-patient subset with septic shock. This model also did not show a statistically significant relationship or trend between etomidate administration and in-hospital mortality (**Table 5**).

DISCUSSION

Although adrenal suppression is consistently noted in patients who receive etomidate (4–11), it is unclear whether transient adrenal suppression has any impact on outcomes. We retrospectively evaluated the safety of etomidate for ICU intubation in over 2,000 patients with sepsis, severe sepsis, or septic shock. These patients reflected a general mixed-diagnosis ICU population, and the cohort size was calculated in advance to detect a 7% difference in survival at an overall anticipated mortality rate of 37.5%. Although not perfectly matched, no clinically important differences existed between the groups, and no association of etomidate was noted with overall in-hospital survival, vasopressor use, duration of mechanical ventilation, ICU LOS, or hospital LOS. Even in the sickest subgroup, those with septic shock, etomidate was not associated with mortality.

Our findings differ significantly from the subgroup analyses in CORTICUS and KETASED (5, 7). In CORTICUS, randomization was to steroids, rather than to etomidate, and the univariate observation that etomidate was associated with higher mortality in the septic cohort (42.7% vs. 30.5%, $p = 0.02$) did not accommodate severity of illness or other potential confounders (5). Although baseline SOFA scores in the groups were similar, the multivariate models did not consider the baseline blood pressure measurements or vasopressor use, and it is possible that the patients in CORTICUS who received etomidate may have been sicker than the cohort intubated with other agents. Etomidate is reputed to be less hemodynamically active than many other intubating agents, and it may be that patients receiving etomidate for intubation in this study had more severe shock before receiving the drug, as supported by the trend away from postintubation propofol use. CORTICUS data included only 96 patients intubated with etomidate when compared with 403 intubated with other agents, although the severity of illness (median SAPS score of 48 and overall mortality of 32.7%) was high (5).

The KETASED trial randomized critically ill patients requiring prehospital or emergency department intubation to receive either etomidate or ketamine—all patients additionally received succinylcholine, midazolam, and fentanyl (7). Their hypothesis was that ketamine, an agent with limited hemodynamic activity in most patients, might be safer for intubation. One third of the patients in KETASED died after randomization but before hospitalization, and ultimately data from only 469 patients of the original 655 patient cohort were evaluated. Of 469 patients, 18% and 15% of those receiving etomidate and ketamine, respectively, were described as septic. Overall

TABLE 4. Regression Model for In-Hospital Mortality in Patients With Sepsis, Severe Sepsis, and Septic Shock ($n = 2014$)

Parameter	Subhazard Ratio	95% Confidence Interval
Etomidate	0.91	0.79–1.05
Age (per year)	1.01	1.01–1.02[a]
Female (reference = male)	0.97	0.84–1.12
Race (reference = Caucasian)		
African American	1.28	1.00–1.64[b]
Other race	1.16	0.93–1.43
Acute Physiology and Chronic Health Evaluation IV score (per unit)	1.01	1.01–1.02[a]
Comorbidities		
Cirrhosis	1.40	0.85–2.29
Diabetes	0.77	0.64–0.93[c]
Hepatic failure	1.18	0.75–1.87
Immunosuppresion	1.36	0.99–1.85
Leukemia	1.57	1.06–2.32
Lymphoma	0.94	0.47–1.89
Metastatic cancer	1.69	1.19–2.40[c]
Myocardial infarction within past 6 mos	1.22	0.55–2.71
Fludrocortisone within 24 hrs before intubation	0.62	0.26–1.49
Hydrocortisone and/or dexa methasone within 24 hrs before intubation	1.32	1.03–1.69
Prednisone, prednisolone, methylprednisolone within 24 hrs before intubation	1.17	0.97–1.41

[a] $p < 0.001$.
[b] $p < 0.05$.
[c] $p < 0.01$.

TABLE 5. Regression Model of In-Hospital Mortality in Patients With Septic Shock ($n = 650$)

Parameter	Subhazard Ratio	95% Confidence Interval
Etomidate	0.87	0.69–1.10
Age (per year)	1.01	1.00–1.02[a]
Female (reference = male)	0.94	0.75–1.18
Race (reference = Caucasian)		
African American	1.20	0.79–1.82
Other race	1.04	0.72–1.48
Acute Physiology and Chronic Health Evaluation IV score (per unit)	1.01	1.01–1.02[b]
Comorbidities		
Cirrhosis	0.67	0.27–1.67
Diabetes	0.71	0.52–0.96[c]
Hepatic failure	1.89	0.87–4.11
Immunosuppresion	1.86	1.12–3.12[c]
Leukemia	1.43	0.70–2.91
Lymphoma	0.60	0.19–1.94
Metastatic cancer	1.23	0.69–2.20
Myocardial infarction within past 6 mos	1.45	0.66–3.19
Fludrocortisone within 24 hrs before intubation	0.91	0.25–3.33
Hydrocortisone and/or dexamethasone within 24 hrs before intubation	1.21	0.83–1.77
Prednisone, prednisolone, methylprednisolone within 24 hrs before intubation	1.15	0.86–1.55

[a] $p < 0.01$.
[b] $p < 0.001$.
[c] $p < 0.05$.

severity of illness (mean SAPS score 50.8) and mortality (median mortality 33%) were similar to patients in our evaluation. In KETASED, adrenal insufficiency was more common in patients intubated with etomidate, and in the very small group of patients with sepsis ($n = 76$) the relative risk of death in those receiving etomidate was 1.4 and did not achieve statistical significance (7).

Our study has several potential weaknesses. First, although data were prospectively entered into the *e*ICU database, our evaluation was retrospective, and some patients may have been misclassified as having not received etomidate. Nonetheless, we diligently strove to eliminate any incorrectly classified patients by excluding those hospitalized at centers where an automated medication interface was absent, and by eliminating those not intubated in the ICU, where medication administration and hemodynamic fluctuations are routinely documented. In addition, we powered the study to allow for a modest (10%) rate of misclassification. This insistence on ICU intubation limits the generalizability of our findings to similar patients, as the clinical characteristics of patients intubated in the emergency department, prehospital environment, or operating room may be fundamentally different from those we studied.

Second, the cohorts were imperfectly matched. Closer evaluation, however, suggests the etomidate group may actually have been sicker—they were older, had a lower mean baseline

blood pressure, and received more steroids before intubation, all of which should have biased the data toward worse outcomes. Conversely, patients who received etomidate were more likely to have been treated in academic medical centers—a potential source of confounding. Adding academic status to the multivariable model, however, did not alter any outcome of interest. Our study lacked any evaluation of the adrenal axis, so we cannot hypothesize how adrenal function relates to our outcomes measures, although a lack of effect of exogenous corticosteroid replacement on outcome was noted. Because of limitations inherent in the dataset, we were also limited to a primary outcome measure of in-hospital mortality, where 28-day or longer outcome data would have been superior.

All retrospective observational research, no matter how well adjusted for confounding influences, is vulnerable to residual confounding, and this study is no different. Given the striking lack of association we observed between etomidate and hospital mortality, however, those uncaptured factors would have to have an overwhelming effect to hide an association between etomidate use and hospital mortality. We believe this is unlikely. Furthermore, we believe severity of illness was adequately adjusted for using APACHE IV scoring, and because our analysis of blood pressure measurements and vasopressor use was conducted in an extremely granular dataset.

One aspect of this study that may limit generalizability of the data is that patients who were intubated in the emergency department or other settings outside of the primary treatment ICU were excluded. We were also unable to include patients intubated without either etomidate or a neuromuscular blockade agent because receiving one was necessary to verify intubation occurred in the ICU. This eliminated many patients who may have been intubated with analgesics, sedatives, and/or dissociative agents without neuromuscular blockade. It also introduces uncertainty about the generalizability of these data to patients who do not receive neuromuscular blockade as part of the induction sequence. Finally, it should be noted that the years from 2008 to 2010 reflect a period of changing practice as regards corticosteroid usage in septic shock—many of our patients received adjunct corticosteroids either before or after intubation, and the effect of these agents as well as the evolution of such practices on the primary outcome variable is unknown.

CONCLUSIONS

Single-dose etomidate for intubation was not associated with hospital mortality, increased vasopressor requirements, longer duration of mechanical ventilation, ICU LOS, or hospital LOS in a large cohort of patients with sepsis, severe sepsis, and septic shock.

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APPENDIX 1. 20 Most Frequent Admission Diagnoses Stratified by Etomidate Receipt

Diagnosis	*n*	%
Top 20 admission diagnoses among all septic patients ($n = 2014$)		
Sepsis, pulmonary	322	16
Pneumonia, bacterial	213	10.6
Pneumonia, other	166	8.2
Sepsis, unknown	149	7.4
Sepsis, renal/UTI (including bladder)	143	7.1
Sepsis, other	112	5.6
Sepsis, GI	98	4.9
Respiratorymedical, other	91	4.5
Sepsis, cutaneous/soft tissue	47	2.3
Arrest, respiratory (without cardiac arrest)	44	2.2
Emphysema/bronchitis	35	1.7
CHF	31	1.5
Cardiac arrest (with or without respiratory arrest; for respiratory arrest, see respiratory system)	27	1.3
Pneumonia, aspiration	26	1.3
ARDS, noncardiogenic pulmonary edema	24	1.2
Pneumonia, viral	24	1.2
Renal failure, acute	23	1.1
Rhythm disturbance (atrial, supraventricular)	21	1
Coma/change in level of consciousness (for hepatic see GI, for diabetic see endocrine, if related to car diac arrest, see CV)	19	0.9
Pancreatitis	16	0.8
Top 20 admission diagnoses among septic patients who received etomidate ($n = 1102$)		
Sepsis, pulmonary	166	15.1
Pneumonia, bacterial	120	10.9
Pneumonia, other	88	8.0
Sepsis, unknown	85	7.7
Sepsis, renal/UTI (including bladder)	78	7.1
Sepsis, other	71	6.4
Sepsis, GI	52	4.7
Respiratorymedical, other	49	4.4
Emphysema/bronchitis	22	2
Sepsis, cutaneous/soft tissue	22	2
Arrest, respiratory (without cardiac arrest)	20	1.8
CHF	19	1.7
Renal failure, acute	18	1.6
Pneumonia, aspiration	14	1.3
Pneumonia, viral	14	1.3

(*Continued*)

APPENDIX 1. (*Continued*) 20 Most Frequent Admission Diagnoses Stratified by Etomidate Receipt

Diagnosis	*n*	%
ARDS, noncardiogenic pulmonary edema	12	1.1
Rhythm disturbance (atrial, supraventricular)	12	1.1
Pancreatitis	11	1
Coma/change in level of consciousness (for hepatic see GI, for diabetic see endocrine, if related to car diac arrest, see CV)	10	0.9
Cardiovascular medical, other	9	0.8
Top 20 admission diagnoses among septic patients who did not receive etomidate ($n = 912$)		
Sepsis, pulmonary	156	17.1
Pneumonia, bacterial	93	10.2
Pneumonia, other	78	8.6
Sepsis, renal/UTI (including bladder)	65	7.1
Sepsis, unknown	64	7
Sepsis, GI	46	5
Respiratorymedical, other	42	4.6
Sepsis, other	41	4.5
Sepsis, cutaneous/soft tissue	25	2.7
Arrest, respiratory (without cardiac arrest)	24	2.6
Cardiac arrest (with or without respiratory arrest; for respiratory arrest see respiratory system)	22	2.4
Emphysema/bronchitis	13	1.4
ARDS noncardiogenic pulmonary edema	12	1.3
CHF	12	1.3
Pneumonia, aspiration	12	1.3
Pneumonia, viral	10	1.1
Coma/change in level of consciousness (for hepatic see GI, for diabetic see endocrine, if related to car diac arrest, see CV)	9	1
Rhythm disturbance (atrial, supraventricular)	9	1
Diabetic ketoacidosis	8	0.9
Bleeding, upper GI	7	0.8

UTI = urinary tract infection; GI = gastrointestinal; CHF = congestive heart failure; ARDS = adult respiratory distress syndrome; CV = cardiovascular.