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Original Contribution

Risk factors for mortality in septic patients who received etomidate ☆

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ABSTRACT

Purpose: To characterize risk factors for mortality in septic patients who received etomidate for rapid sequence intubation.

Materials and Methods: This study was a retrospective cohort conducted at a large, tertiary, urban, academic medical center that included patients with severe sepsis or septic shock who received etomidate between January 1, 2010, and December 31, 2012.

Results: A total of 169 patients were included with similar baseline characteristics. There were more men in the nonsurvivor group than in the survivor group (67.1% vs 50.6%, $P = .03$). Septic shock occurred in 91.5% of nonsurvivors and 69% of survivors ($P < .01$). Nonsurvivors also had a higher initial lactate of (5.1 ± 4.3 mmol/L vs 3.6 ± 3.4 mmol/L, $P = .02$) and more vasopressor therapy (91.5% vs 69%, $P < .01$), required a higher number of vasopressors (2.2 ± 1.1 vs 1.3 ± 1, $P < .01$), and were administered hydrocortisone (53.7% vs 34.5%, $P = .01$). Abdominal source of sepsis ($P = .048$) and number of vasopressors ($P = .01$) were predictive of 30-day mortality.

Conclusion: An alternative sedative induction agent may be considered for use in rapid sequence intubation in patients on multiple vasopressors or with abdominal source of infection.

1. Introduction

Etomidate is a sedative commonly used for rapid sequence intubation (RSI). A single dose produces sedation within minutes with minimal effect on hemodynamic parameters, making it an attractive agent for patients presenting with sepsis or septic shock [1]. However, etomidate suppresses cortisol production through inhibition of adrenal mitochondrial 11-β-hydroxylase activity, leading to adrenal suppression after a single dose [2]. Although the definition of adrenal insufficiency (AI) in sepsis remains debated [3], the degree of AI in patients with septic shock has been shown to correlate with incidence of mortality [4]. Furthermore, etomidate was withdrawn from the market as a continuous infusion sedative due to reports of increased mortality. After a bolus dose of etomidate, AI may persist for up to 48 hours in critically ill patients [5]. Despite this connection between etomidate and AI, evidence demonstrating that AI secondary to etomidate use in septic patients actually increases mortality is conflicting.

In a randomized controlled trial of 655 critically ill patients who received etomidate vs ketamine for RSI, the etomidate group had a significantly higher rate of AI (86% of 116 etomidate recipients vs 48% of 116 ketamine recipients, $P < .0001$). However, this did not translate into increased morbidity or mortality in the etomidate group, including the subgroup of patients presenting with sepsis (mortality: 41.5% etomidate vs 34.3% ketamine; odds ratio [OR], 1.4; 95% confidence interval [CI], 0.5-3.5) [6]. This was also reported in smaller randomized controlled study comparing etomidate to midazolam, which showed no difference in length of stay or mortality [7]. However, neither of these studies was powered to detect a difference in mortality. Several observational or retrospective studies have also evaluated etomidate use in septic patients compared with other RSI agents, and again a significant difference in morbidity and mortality in the etomidate group was not observed [8–11].

Recently, a meta-analysis of patients pooled from randomized controlled trials and observational studies assessed the effects of etomidate on AI and all-cause mortality [12]. Five studies with a total of 865 patients were evaluated for the mortality end point. Etomidate patients were more likely to experience mortality compared with other induction agents (pooled relative risk, 1.20; 95% CI, 1.02-1.42). Seven studies of 1303 patients showed that etomidate administration increased the likelihood of developing AI (pooled relative risk, 1.33; 95% CI, 1.22-1.46). Due to lack of a consensus and conflicting data as to whether etomidate should be given to patients with sepsis, we conducted a retrospective review of septic patients who received etomidate and who experienced mortality compared with those who did not in order to

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characterize septic patients that should not receive etomidate by identifying independent risk factors for mortality.

2. Materials and methods

2.1. Study design and participants

This is a retrospective, cohort study evaluating patients with severe sepsis or septic shock who developed respiratory failure and received etomidate for RSI. This single-center study was conducted at a 535-bed academic medical center located in the suburbs of Chicago, IL. This study was approved by the institutional review board.

All patients located in the emergency department or admitted to the surgical or medical intensive care units (ICUs) between January 1, 2010, and December 31, 2012, were considered for inclusion. Inclusion criteria were patients age 18 years or older, diagnosis of severe sepsis or septic shock, and having received a single-dose etomidate for RSI. Patients were excluded if etomidate was given for a surgical procedure or if they were on baseline corticosteroids (≥5 mg prednisone or equivalent). It was anticipated that over the 2-year study period, 200 patients would meet the inclusion criteria and be included in this study.

2.2. Data collection

Data were extracted from the electronic medical record for patients meeting the inclusion criteria. Baseline variables were collected, which included age, sex, race, admitting service, severe sepsis or septic shock diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, medical history of hypertension, end-stage renal disease, coronary artery disease, diabetes, or cerebrovascular accident. Further data collected included etomidate dose, concomitant RSI medications (ie, succinylcholine, rocuronium), source of infection and pathogen, initial lactate level, vasopressor use, hydrocortisone administration, cortisol levels, and mortality.

2.3. Outcome measures

The primary aim of this study was to identify independent risk factors for mortality in septic patients who received etomidate for RSI by comparing those who experienced mortality to those who did not. In addition, the effects of etomidate on vasopressor and hydrocortisone requirements in patients who develop septic shock will be evaluated.

2.4. Statistical analyses

Means, standard deviations, and percentages were calculated for baseline variables. Comparisons of continuous variables were done using a *t* test. A χ^2 test or Fisher exact test was used to compare categorical variables as appropriate. A bivariate analysis was performed to assess differences between patients who experienced mortality vs those who did not. A *P* value less than .05 was considered significant. A multivariate logistic regression was used to account for confounding variables and to identify independent risk factors for mortality in patients with sepsis who received etomidate during RSI. Variables from the univariate analysis with a significance of $P \leq .2$ were evaluated for inclusion in the multivariate analysis. Microsoft Excel software (Redmond, WA) and SPSS version 20 (Chicago, IL) was used for data analysis.

3. Results

Overall, 178 patients were identified via *International Classification of Diseases, Ninth Revision* codes for sepsis and RSI, of which 7 were excluded for intubation not related to sepsis and 2 were excluded for non-etomidate sedative use. A total of 169 patients were included in the analysis, 87 survivors and 82 nonsurvivors.

Baseline characteristics were similar between study groups (Table 1). There was a higher percentage of men in the nonsurvivor group than in the survivor group (67.1% vs 50.6%, $P = .03$). Septic shock occurred in 91.5% of nonsurvivors and 69% of survivors ($P < .01$). Nonsurvivors also had a higher initial lactate of 5.1 ± 4.3 mmol/L in comparison to 3.6 ± 3.4 mmol/L in survivors ($P = .02$). More nonsurvivors than survivors required vasopressor therapy (91.5% vs 69%, $P < .01$), a higher number of vasopressors (2.2 ± 1.1 vs 1.3 ± 1, $P < .01$), and were administered hydrocortisone (53.7% vs 34.5%, $P = .01$). Succinylcholine was administered to 54.9% of nonsurvivors and 75.9% of survivors ($P < .01$). Of the survivors, 37 (40.2%) had baseline cortisol levels, compared with 37 (45.1%) of nonsurvivors. There was no difference in baseline cortisol levels between groups (25.9 vs 31.3 μg/dL, $P = .28$). Only 6 survivors (6.9%) and 5 nonsurvivors (6.1%) had multiple cortisol levels with an adrenocorticotropic hormone 250 μg test performed. Of those patients tested, all had a rise in cortisol levels to at least 18 to 20 μg/dL.

Backward, stepwise multivariate logistic regression was conducted. Variables included in the analysis were initial lactate at least 4 mmol/L, type of sepsis, paralysis with succinylcholine, paralysis with rocuronium, abdominal source, APACHE II score, and number of vasopressors. Abdominal source ($P = .048$) and number of vasopressors ($P < .01$) were predictive of 30-day mortality in patients who received etomidate for induction during RSI (Table 2). Patients with higher vasopressor requirements had increased odds of 30-day mortality (OR, 7.09; 95% CI,

Table 1
Baseline characteristics

Characteristic	Survivors (n = 87)	Nonsurvivors (n = 82)	*P*
Age (y), mean ± SD	62.1 ± 17.3	64.1 ± 15.7	.45
Sex, male, n (%)	44 (50.6)	55 (67.1)	.03
Race, n (%)			.72
African American	23 (26.4)	19 (23.2)	
White	52 (59.8)	54 (65.9)	
Hispanic	7 (8)	7 (8.5)	
Unit, n (%)			.63
Medical ICU	65 (74.7)	62 (75.6)	
Surgical ICU	19 (21.8)	19 (23.2)	
APACHE II, mean ± SD	22.4 ± 8.7	26 ± 10.4	.11
Comorbid conditions, n (%)			
DM	42 (48.3)	42 (51.2)	.7
HTN	45 (51.7)	44 (53.7)	.8
CKD	23 (26.4)	27 (32.9)	.36
CAD	20 (23)	19 (23.2)	.98
CVA	5 (5.7)	7 (8.5)	.48
Septic shock, n (%)	60 (69)	75 (91.5)	<.01
Initial lactate, mean ± SD	3.6 ± 3.4	5.1 ± 4.3	.02
Lactate > 4 mmol/L, n (%)	19 (38)	33 (52.4)	.12
Etomidate dose (mg), mean ± SD	17.3 ± 8.4	17.3 ± 9	.6
Etomidate dose (mg/kg), mean ± SD	0.24 ± 0.24	0.24 ± 0.24	0.72
Source of infection, n (%)			
CNS	6 (6.9)	1 (1.2)	.06
Pneumonia	43 (49.4)	31 (37.8)	.13
Abdominal	12 (13.8)	23 (28)	.02
Genitourinary	11 (12.6)	6 (7.3)	.25
Skin	1 (1.1)	1 (1.2)	.97
Bacteremia	15 (17.2)	21 (25.6)	.18
Other	2 (2.3)	0 (0)	.17
Unknown	4 (4.6)	6 (7.3)	.45
Cortisol[a], mean ± SD	25.9 ± 21.1	31.3 ± 20.5	.28
Vasopressors, n (%)	60 (69)	75 (91.5)	<.01
No. of vasopressors, mean ± SD	1.3 ± 1	2.2 ± 1.1	<.01
Inotropes, n (%)	6 (7)	11 (13.4)	.17
Hydrocortisone, n (%)	30 (34.5)	44 (53.7)	.01
Succinylcholine, n (%)	66 (75.9)	45 (54.9)	<.01
Rocuronium, n (%)	18 (20.7)	27 (32.9)	.07

This table displays baseline characteristics between survivors and nonsurvivors. Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CNS, central nervous system; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension.

[a] n = 37 (40.2%) survivors vs n = 37 (45.1%) nonsurvivors.

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