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Effects of etomidate on vasopressor use in patients with sepsis or severe sepsis: A propensity-matched analysis☆,☆☆

Nerissa J. Alday, PharmD [b], G. Morgan Jones, PharmD, BCPS [c], Lauren A. Kimmons, PharmD, BCPS [c], Gary S. Phillips, MAS [d], Jennifer W. McCallister, MD [e,f], Bruce A. Doepker, PharmD, BCPS [a,*]

[a] Department of Pharmacy, Wexner Medical Center at Ohio State University, Columbus, OH 43210-1228
[b] Department of Pharmacy, Nationwide Children's Hospital, Columbus, OH 43205
[c] Methodist University Hospital, University of Tennessee College of Pharmacy, Memphis, TN 38104
[d] Center for Biostatistics, Ohio State University, Columbus, OH 43221
[e] Department of Internal Medicine, Wexner Medical Center at Ohio State University, Columbus, OH 43221
[f] Pulmonary, Allergy, Critical Care and Sleep Medicine, Davis Heart and Lung Research Institute, Columbus, OH 43210-1267

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ABSTRACT

Purpose: The safety of single-bolus etomidate to facilitate intubation in septic patients is controversial due to its potential to suppress adrenal steroidogenesis. The purpose of this study was to evaluate the effects of etomidate on the development of shock when used as an induction agent to facilitate intubation in septic patients.

Methods: A multicenter, retrospective, propensity-matched cohort study comparing patients with sepsis or severe sepsis who either received etomidate or did not receive etomidate for intubation was conducted. The primary outcome was the difference in the need for vasopressor support within 72 hours after intubation. Secondary outcomes included the use of multiple vasopressors, intensive care unit length of stay, and in-hospital mortality.

Results: A total of 411 patients were analyzed. Eighty-three patients were matched by propensity score. There was no difference in the matched cohort in regards to vasopressor use within 72 hours of intubation (odds ratio, 0.95; 95% confidence interval, 0.52-1.76; $P = .88$). Furthermore, there were no significant differences observed with regard to secondary outcomes, including in-hospital mortality ($P = .76$).

Conclusions: The use of etomidate for intubation in septic patients did not increase vasopressor requirements within 72 hours after intubation.

1. Background

Etomidate is an imidazole sedative-hypnotic agent used to facilitate intubation. It has a rapid, predictable onset of action and recovery time compared with other induction agents. Historically, etomidate has been a favorable agent for use in patients with hemodynamic compromise due to its low rate of cardiovascular side effects and minimal risk of respiratory depression [1-3]. However, recent literature has created controversy regarding the use of etomidate in patients with hemodynamic compromise secondary to sepsis because of its potential to induce adrenal insufficiency and increase the risk of hypotension.

Etomidate is known to suppress adrenal steroidogenesis for up to 72 hours after a single dose through the inhibition of 11-β-hydroxylase, a key enzyme involved in the conversion of deoxycortisol to cortisol [2-7].

In septic patients, this inhibition may blunt cortisol production that is stimulated by activation of the hypothalamic-pituitary-adrenal axis. Because septic patients attempt to maintain vascular homeostasis by mounting a compensatory adrenal stress response, those receiving etomidate may be at an increased risk for refractory hypotension. Several large studies of septic patients have raised concern over the association between etomidate-related adrenal insufficiency and increased mortality; however, these studies were not adequately designed to evaluate this outcome [2,8-12]. More recent retrospective studies have failed to reproduce these earlier findings [7,13-16]. There is also a lack of quality evidence evaluating outcomes such as vasopressor use and hypotension associated with etomidate-related adrenal insufficiency in patients with sepsis and severe sepsis. Published studies that have reported hemodynamic outcomes associated with single-bolus etomidate have been primarily observational in nature and included small patient populations with severe sepsis and septic shock [7,13,14,16,17].

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* Corresponding author. Department of Pharmacy, Wexner Medical Center at Ohio State University, Columbus, OH; 410 W. 10th Ave, Room 368 Doan Hall, Columbus, OH 43210-1228. Fax: +1 614 293 3165.
E-mail address: Bruce.Doepker@osumc.edu (B.A. Doepker).

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The impact of single-bolus dose etomidate on outcomes such as vasopressor use, hypotension, and mortality in patients with sepsis or severe sepsis remains to be fully characterized. This study serves as the first propensity-matched study designed to evaluate the hemodynamic consequences of etomidate use before progression to septic shock. The primary objective was to further define the association between etomidate use and postintubation vasopressor requirements among patients with sepsis or severe sepsis.

2. Methods

2.1. Study design

A retrospective, multicenter propensity-matched cohort study of patients with sepsis or severe sepsis was performed at the Ohio State University Wexner Medical Center, a 1200-bed academic tertiary care institution in Columbus, OH, and Methodist University Hospital, a 660-bed community academic medical center in Memphis, TN. Patients were eligible for inclusion if they were between the ages of 18 and 89 years, had a diagnosis of suspected or confirmed sepsis or severe sepsis, and were intubated at either institution between January 1, 2007, and October 31, 2012. Exclusion criteria included incarceration, pregnancy, history of chronic adrenal insufficiency, vasopressor use within 24 hours before intubation, corticosteroid use within 30 days before intubation, history of chronic immunosuppression (including HIV/AIDS, chemotherapy, radiation therapy, or transplant immunosuppressive therapy within 30 days before intubation), hypersensitivity to etomidate, or an advanced directive to withhold or withdraw life-sustaining treatment before intubation. This study was approved by institutional review boards at Wexner Medical Center and the University of Tennessee Health Sciences Center.

2.2. Data collection and measurement

Patients were identified using an electronic database at both medical centers to select for patients with *International Classification of Diseases*, *Ninth Revision* (*ICD-9*), codes for diagnoses of sepsis or severe sepsis and mechanical ventilation. Chart review using electronic medical records and paper charts was used to screen patients for inclusion and to extract information for analysis. The following baseline variables were recorded within 24 hours before intubation: demographics, presence of sepsis or severe sepsis criteria, source of infection, community-acquired infection or health care–associated infection, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Scale (GCS) score. Vital signs included baseline mean arterial pressure (MAP) and systolic blood pressure (SBP) within 2 hours before intubation as well as the lowest reported MAP and SBP within 0 to 12, 12 to 24, 24 to 48, and 48 to 72 hours postintubation. Additional data included induction agent(s) and dose (s) administered, vasopressor (epinephrine, norepinephrine, phenylephrine, dopamine, or vasopressin) use and maximum infusion rates within 72 hours postintubation, duration of mechanical ventilation, hospital and intensive care unit (ICU) length of stay (LOS), all-cause mortality, serum cortisol levels, and postintubation corticosteroid use. The decision to intubate, choice of agents for induction, use of vasopressors, and use of corticosteroids were left to the treating physician's discretion.

2.3. Study outcomes

The primary study outcome was the need for vasopressor support within 72 hours postintubation. Secondary outcome measures included incidence of postintubation hypotension, use of multiple vasopressors within 72 hours postintubation, total duration of vasopressor use, time to vasopressor initiation, time to vasopressor withdrawal, duration of mechanical ventilation, ICU and hospital LOS, and all-cause mortality.

2.4. Definitions

The criteria for sepsis and severe sepsis followed those defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [18,19]. Adrenal insufficiency was determined by nonresponse to corticotropin stimulation test as defined by an increase in serum cortisol level of less than 9 μg/dL or a random cortisol level of less than 15 μg/dL [8,10]. A health care–associated infection was defined by the American Thoracic Society/Infectious Diseases Society of America [20]. *Community-acquired infection* was defined as an infectious process that failed to meet the criteria for health care–associated infection. Initiation of appropriate empirical antibiotics was defined by the start of antimicrobial regimens for which presumptive or definitive pathogens were susceptible to in vitro. In the case of culture-negative sepsis or severe sepsis, broad spectrum antibiotics were deemed appropriate based on the presumptive source of infection and in accordance with local practice guidelines [21]. Indications for intubation included respiratory compromise, hemodynamic collapse, altered neurologic status (eg, inability to protect the airway), or trauma as documented in electronic or paper chart intubation notes. Hypotension was defined by a MAP decrease of more than 40% and MAP of less than 70 mm Hg, an MAP of less than 60 mm Hg, or SBP of less than 90 mm Hg lasting more than 15 minutes despite 500- to 1000-mL intravenous fluid bolus, initiation of vasopressor, or increment of more than 30% of the vasopressor dose [14]. Use of multiple vasopressors was defined by the initiation of more than 1 vasopressor with at least 1 vasopressor running at the maximum infusion rate within 72 hours postintubation. Maximum infusion rates were as follows: epinephrine, 1 μg/kg per minute; norepinephrine, 3.3 μg/kg per minute; phenylephrine, 9 μg/kg per minute; dopamine, 20 μg/kg per minute; or vasopressin, 0.1 U/min. The time to vasopressor initiation was determined as the time from intubation to initiation of the first vasopressor, whereas the time to vasopressor withdrawal was defined as the time from intubation to discontinuation of all vasopressors for at least 24 hours.

2.5. Statistical analysis

Descriptive statistics were used to report demographic and other baseline characteristics. χ^2 Test or Fisher exact test was used to analyze categorical data. Continuous data were analyzed using the Student *t* test for parametric data, whereas Wilcoxon rank sum test was used for nonparametric continuous data. Logistic regression was used to generate a propensity score (logit) for each subject. This score was matched 1:1 between those receiving and not receiving etomidate using a random seed, nearest neighbor (caliper $\leq$0.25), without replacement [22]. Results are reported for continuous variables as the median (interquartile range) for nonparametric data or mean $\pm$ SD for parametric data and for categorical variables as frequency distributions. A 2-sided $P < .05$ was considered statistically significant.

The study sample size was calculated to achieve at least 80% power to detect a 25% difference in vasopressor use between the groups using an α value of .05. Approximately 300 etomidate and 100 nonetomidate patients were needed to match 70 patients between the groups. Patients who died or were discharged within 72 hours were included in this intention-to-treat analysis.

Propensity score matching was used to adjust for baseline differences and minimize bias between patients who received etomidate for intubation and patients who did not receive etomidate. Variables included in the propensity score calculation were age, sex, weight, indication for intubation, location of intubation, APACHE II