CJEM Journal Club

Safety of etomidate bolus administration in patients with septic shock

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Clinical questions

1. In critically ill patients with septic shock, does exposure to bolus administration of etomidate increase the risk of inadequate response to corticotropin and mortality compared to no exposure?
2. In critically ill patients with septic shock who are exposed to bolus administration of etomidate, does hydrocortisone reduce the risk of death compared to placebo?

Article chosen

Cuthbertson BH, Sprung CL, Annane D, et al. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. *Intensive Care Med* 2009;35:1868-76.

Study objective

The authors sought to test the hypotheses that bolus doses of etomidate results in an increased proportion of nonresponders to corticotropin and an increase in mortality and that hydrocortisone treatment decreases mortality in patients receiving etomidate.

Keywords: adrenal insufficiency, emergency airway management, etomidate, sepsis

BACKGROUND

Etomidate is commonly used to achieve induction-level sedation prior to endotracheal intubation because of its cardiovascular stability, rapid onset and short duration, and cerebroprotective properties.[1–3] However, critical illness–related corticosteroid insufficiency has been associated with etomidate after the administration of a single dose.[4,5]

Critical illness–related corticosteroid insufficiency, commonly referred to as adrenal insufficiency, is defined as inadequate cellular corticosteroid activity for the severity of the patient's illness. It is best diagnosed by a delta serum cortisol of less than 248 nmol/L after administration of cosyntropin 250 μg or a random total serum cortisol of less than 276 nmol/L.[6] Adrenal insufficiency has been associated with increased mortality in septic shock.[7] Investigations into the utility of hydrocortisone replacement in these patients have yielded mixed results. One study suggested that corticosteroid replacement was beneficial, whereas another demonstrated an equivocal result.[8,9] Several guidelines have recommended that corticosteroid replacement therapy be considered in patients with adrenal insufficiency who have refractory septic shock.[10,11] The use of etomidate to facilitate emergency endotracheal intubation in patients with septic shock is particularly concerning as the potential for etomidate to contribute to adrenal insufficiency may result in adverse patient outcomes. Etomidate use in this situation may avoid peri-intubation hemodynamic instability in the short term yet result in increased patient mortality in the longer term. There is no study to date demonstrating that the use of etomidate leads to an increase in mortality or morbidity.[12]

In the study being reviewed, Cuthbertson and colleagues sought to determine whether etomidate

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exposure in patients with septic shock was associated with an increased incidence of inadequate response to corticotropin and 28-day mortality.[13] They also aimed to determine whether corticosteroid replacement reduced mortality in patients exposed to etomidate.

STUDY DESIGN AND PATIENT POPULATION

This was an a priori substudy of the prospective, randomized, double-blind, placebo-controlled Corticosteroid Therapy of Septic Shock (CORTICUS) study.[9] The CORTICUS study randomized 499 adult patients with septic shock to receive hydrocortisone 50 mg IV or placebo every 6 hours. As part of the study design, etomidate use was discouraged because of its potential for adrenal suppressive effects but did not constitute an exclusion criterion. Approximately 90% of patients enrolled required mechanical ventilation. No breakdown was provided in terms of proportions requiring invasive versus noninvasive mechanical ventilation. The study was stopped prematurely (target N = 800) as recruitment was hampered by the widespread use of corticosteroid replacement therapy. Analysis of the 499 patients recruited found no difference in 28-day mortality between groups. However, patients who received hydrocortisone were able to be liberated from vasopressor support approximately 3 days earlier than those in the placebo group.

The cohort of patients of interest was those who received any dose of etomidate via bolus administration within 72 hours prior to being randomized to receive hydrocortisone or placebo. This time cutoff was prospectively chosen because the authors believed these patients to be most likely to develop an inadequate response to corticotropin, representing adrenal insufficiency. Patients who were exposed to etomidate more than 72 hours prior to trial inclusion were not included as it was assumed that the effects (if any) would not persist beyond 3 days.

OUTCOME MEASURES

Study end points in the etomidate-exposed patients included short corticotropin stimulation test response, 28-day mortality, and 28-day mortality in patients who received hydrocortisone. Inadequate response to corticotropin was defined as a failure of serum cortisol concentrations to increase more than 248 nmol/L after bolus intravenous administration of corticotropin 250 μg.

RESULTS

Ninety-six (96 of 499, 19.2%) patients received etomidate within 72 hours of randomization in the CORTICUS study and were included for analysis. A further 33 (7%) patients who had received etomidate met the exclusion criteria stated above. The median time between etomidate exposure and randomization to hydrocortisone or placebo was 14.5 hours (interquartile range 4.25–28.4), but reasons for etomidate use and total dose administered were not reported.

Baseline characteristics including age, gender, race, severity of illness, and cardiovascular component of the Sequential Organ Failure Assessment (SOFA) score were similar between the etomidate-exposed group and those who were not exposed to the drug. However, baseline serum cortisol concentration appeared lower in the etomidate group (559 nmol l^{1} vs 713 nmol l^{1}; no p value reported). Patients who had been exposed to etomidate were also more likely to have an inadequate response to corticotropin than those who were not exposed (61.0% vs 44.6%, absolute risk increase 16.4%, number needed to harm [NNH] 6, p = 0.004).

Univariate analysis revealed an association between etomidate exposure and mortality (OR = 1.7, 95% CI 1.07–2.68; NNH 8, 95% CI 4–68; p = 0.02), but no difference was seen between groups in terms of causes of death. Logistic regression models were explored to control for confounders, with the first adjusting for treatment group, corticotropin response, baseline cortisol value, and Simplified Acute Physiology Score II (SAPS II). This model did not reveal a significant association between etomidate exposure and increased mortality (OR = 1.60, 95% CI 0.98–2.62; p = 0.06). However, when the SOFA score was incorporated into the model, a statistically significant association between etomidate exposure and increased mortality was observed (OR = 1.75, 95% CI 1.06–2.90; p = 0.03). The authors reported that hydrocortisone administration did not attenuate the associated increase in mortality seen in the etomidate-exposed group (45.1% vs 40% in the hydrocortisone and placebo groups, respectively; no p value reported).

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COMMENTARY

Etomidate for rapid-sequence induction has gained widespread popularity in emergency medicine owing to its ease of administration in combination with a stable cardiovascular profile.[14] Peri-intubation hemodynamic instability is common in the critically ill patient population and is thought to be related in part to medications administered to facilitate intubation.[15] Although medications may be one risk factor for the development of peri-intubation hemodynamic instability, other factors are probably also important.[16,17]

Peri-intubation hemodynamic instability has not been thoroughly evaluated, and little is known about its incidence, risk factors, and impact on patient outcomes.[17] Despite this, evidence exists indicating that both sustained and nonsustained hemodynamic instability in the general emergency department patient population are associated with increased mortality.[18] Critically ill patients requiring resuscitation and emergency endotracheal intubation commonly present with physiologic derangements. Further hemodynamic instability associated with airway management is likely to be poorly tolerated. In light of this, the avoidance or minimization of peri-intubation hemodynamic instability is an important management principle.

High-quality research examining peri-intubation hemodynamic responses to other induction agents used in emergency airway management is minimal. Ketamine has been shown to be similar to etomidate in terms of offering a stable cardiovascular profile when used to facilitate rapid-sequence intubation in critically ill patients.[12] Even though hemodynamic information about other induction agents is lacking, research establishing the risk of etomidate in patients with sepsis should be undertaken.

This was a substudy of a prospective, randomized, placebo-controlled trial and must be interpreted with the cautions associated with observational research. Although in one regression model, an association between etomidate exposure and mortality was established, it does not prove that etomidate caused that increased risk for death. Confounding factors could have accounted for the associated increase in mortality. The patients in this subset were not randomized for this purpose. There was no sample size calculation for this study; given the early termination of the original study, this particular analysis was probably underpowered. There was no description of other medications administered prior to randomization. Unreported patient factors may have contributed to the treating clinician's decision to use etomidate prior to randomization. Reported baseline characteristics between the initial study groups were similar. In this subset of patients determined by criteria (use or nonuse of etomidate) distinct from the original randomization, the two groups were different at baseline. A univariate analysis revealed a modest association between etomidate and 28-day mortality; however, this method of analysis evaluates the relationship between two variables and does not control for interactions with other potential confounding variables.[19] Although the result of one of the multiple regression analyses was statistically significant, the result of another was not. In the positive analysis, the association between etomidate exposure and mortality was modest (OR 1.75). Furthermore, the indications for etomidate administration and details of the dosing regimens administered were not reported. The authors of the source study reported that etomidate was used for induction of anesthesia; however, no specific details were provided.[9] This study's results are discordant with another underpowered subgroup analysis from an earlier study that revealed treatment with etomidate in septic patients was not associated with increased odds of death when compared to ketamine.[12] Both analyses were exploratory and hypothesis generating at best.

A search of ClinicalTrials.gov revealed one actively recruiting prospective, randomized, double-blind, single-centre study comparing etomidate versus midazolam for intubation of patients with sepsis (NCT-00441792). Its aims are to determine the difference in mortality and length of stay between the two groups of critically ill septic patients. The results of this study and those of future prospective, randomized, controlled trials will be required to determine the safety of etomidate bolus administration in patients with septic shock.

CONCLUSION

This study does not provide definitive answers to the clinical questions surrounding risk of use of etomidate for rapid-sequence induction anesthesia in septic shock. The study also does not adequately address the utility of supplemental corticosteroids to counteract potential adverse effects on the hypothalamic-pituitary-adrenal axis.

Competing interests: None declared.

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