CRITICAL CARE

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Etomidate and adrenal insufficiency: the controversy continues

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Expanded Abstract

Citation

Jabre P, Combes X, Lapostolle F, *et al*. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009, 374:293-300. PMID: 19573904

Background

Critically ill patients often require emergency intubation. The use of etomidate as the sedative agent in this context has been challenged because it may cause a reversible adrenal insufficiency, potentially associated with increased in-hospital morbidity. We compared early and 28-day morbidity after a single dose of etomidate or ketamine used for emergency endotracheal intubation of critically ill patients.

Methods

In this randomized, controlled, single-blind trial, 655 patients who needed sedation for emergency intubation were prospectively enrolled from 12 emergency medical services or emergency departments and 65 intensive care units in France. Patients were randomly assigned by a computerized random-number generator list to receive 0·3 mg/kg of etomidate (n = 328) or 2 mg/kg of ketamine (n = 327) for intubation. Only the emergency physician enrolling patients was aware of group assignment. The primary endpoint was the maximum score of the sequential organ failure assessment during the first 3 days in the intensive care unit. We excluded from the analysis patients who died before reaching the hospital or those discharged from the intensive care unit before 3 days (modified intention to treat). This trial is registered with ClinicalTrials.gov, number NCT00440102.

Findings

234 patients were analyzed in the etomidate group and 235 in the ketamine group. The mean maximum SOFA score between the two groups did not differ significantly (10.3 [SD 3.7] for etomidate vs. 9.6 [3.9] for ketamine; mean difference 0.7 [95% CI 0.0-1.4], p = 0.056). Intubation conditions did not differ significantly between the two groups (median intubation difficulty score 1 [IQR 0-3] in both groups; p = 0.70). The percentage of patients with adrenal insufficiency was significantly higher in the etomidate group than in the ketamine group (OR 6.7, 3.5-12.7). We recorded no serious adverse events with either study drug.

Interpretation

Our results show that ketamine is a safe and valuable alternative to etomidate for endotracheal intubation in critically ill patients, and should be considered in those with sepsis.

Commentary

A single dose of etomidate is associated with decreased serum concentrations of cortisol for at least 24 hours after its administration [1,2]. Continuous intravenous administration of etomidate has been associated with adrenocortical dysfunction and increased patient mortality [3-5]. Several studies have suggested an association between etomidate-induced adrenal insufficiency and increased morbidity in the critically ill, particularly in those with sepsis [6,7]. Yet, etomidate continues to be used commonly for rapid sequence intubation as it is less likely to cause hypotension. This favorable cardiovascular profile is important in critically ill patients with severe sepsis. This study was designed to investigate the possibility of a causal relationship between etomodiate use and increased morbidity or mortality. Etomidate was compared to ketamine, which has similar cardiovascular profile, but may be associated with adverse psychiatric events [8].

Jabre et al. conducted a prospective, randomized controlled single-blind trial where subjects requiring intubation were randomized to etomidate (0.3 mg/kg) or ketamine (2 mg/kg) with succinylcholine prior to ICU

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admission. The primary endpoint was the maximum score of the sequential organ failure assessment during the first 3 days in the intensive care unit. Secondary endpoints were identified as organ dysfunction and failure occurring after admission to the intensive care unit (Δ-SOFA), 28-day all-cause mortality, days free from intensive care unit, organ support-free days, and measurement and correlation with adrenal insufficiency. A modified intention-to-treat (ITT) analysis was used, where randomized patients who died before reaching hospital and those discharged from the intensive care unit within 3 days were excluded. This analysis adjusted for age, simplified acute physiology score II, and sex to ensure that these factors were equally distributed between these groups because the modified ITT analysis was performed in 469 of the 655 subjects who were randomized.

The results did not demonstrate any significant differences in mean $SOFA_{max}$ score, 28-day mortality, catecholamine use, median ventilator-free days, and median hospital-free days between the two groups. Since the investigators had specific concerns for patients with severe sepsis or trauma, these populations were identified as subgroups of interest *a priori*; however, no significant differences in maximum SOFA were seen. The investigators did find that the percentage of patients with adrenal insufficiency was significantly higher in the etomidate group (86% vs. 48%, $p < 0.0001$). However, no significant differences in morbidity or mortality were found in those with adrenal insufficiency. The authors concluded that ketamine is a safe and valuable alternative to etomidate and should be considered in those with sepsis. This recommendation seems to be derived from the post hoc analysis of CORTICUS trial [9] suggesting that patients with severe sepsis had a significantly higher 28-day mortality rate if they received etomidate ($p = 0{\cdot}03$).

The strength of this study is the randomized controlled prospective design. Randomization in the modified intention to treat analysis appeared to be complete. It adds to the body of literature suggesting that a single dose of etomidate may be associated with adrenal insufficiency but is not associated with an increase in morbidity or mortality. The weakness of the study is that the design was underpowered to detect differences in the subgroups of interest (patients with trauma and sepsis, n = 180) and it was also underpowered to detect differences in mortality. This study may not be generalizable to inpatients requiring emergent intubation as this study was conducted in the pre-hospital and emergency department setting, where the majority of intubations were performed for "comatose" patients.

In conclusion, this study found no difference in early and 28-day morbidity and mortality after a single dose of etomidate or ketamine used for emergency endotracheal intubation of critically ill patients. This study was unable to answer questions about the impact of etomidate and its related adrenal insufficiency on trauma and sepsis populations and larger randomized controlled trials will be needed.

Recommendations

One bolus of etomidate is not associated with a significant increase in morbidity or mortality compared to ketamine. Etomidate can still be safely be used for rapid sequence intubation.

Competing interests
The authors declare that they have no competing interests.

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