

Should emergency physicians use etomidate for rapid sequence intubation?

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Clinical question

Does the use of etomidate for rapid sequence intubation (RSI) in critically ill patients lead to harm compared to another intravenous induction agent?

Article chosen

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.

Study objective

The study authors sought to determine whether the use of etomidate for emergency department RSI in critically ill adults is associated with greater morbidity or mortality compared to the use of ketamine.

the data demonstrated that the use of etomidate for intubation was associated with a higher incidence of prolonged adrenal suppression^{5,6} and a greater risk of dying than in patients who did not receive etomidate.^{7,8} Jabre and colleagues' randomized controlled trial (RCT) is the first large study in which critically ill patients were randomized to receive etomidate or a comparator induction agent to determine whether the use of etomidate is associated with greater morbidity and mortality.

STUDY DESIGN

This was a double-blinded RCT conducted in 12 emergency medical systems (EMS) in France. Consecutive, critically ill adults requiring urgent RSI were enrolled. All EMS units were staffed with senior emergency physicians (EPs) who intubated eligible patients. Patients were block randomized to etomidate 0.3 mg/kg IV or ketamine 2 mg/kg IV. All patients received succinylcholine 1 mg/kg IV for relaxation. Study drugs were sealed in identically appearing, numbered boxes, and only the EPs enrolling patients were aware of group assignment. All caregivers involved in direct patient care were blinded to treatment allocation.

Patients were excluded if they were in cardiac arrest, were pregnant, or had known contraindications to ketamine, etomidate, or succinylcholine. Patients who did not survive transport to hospital or were discharged

Keywords: adrenal suppression, etomidate, intubation, ketamine, mortality, sepsis

BACKGROUND

Etomidate is the most commonly used induction agent for emergency department (ED) rapid sequence intubation (RSI) in North America.¹ This is likely due to its hemodynamic tolerance, simple dosing profile, lack of histamine release, and lack of immediately apparent side effects.²

In recent years, the safety of etomidate has been questioned because large controlled trials on patients with septic shock have highlighted the importance of an intact pituitary-adrenal axis in critical illness.^{3,4} Although none of these studies randomized patients,

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within 3 days of admission to the intensive care unit (ICU) were excluded from the analysis. This a priori defined modified intention-to-treat (mITT) analysis was conducted to ensure a narrow spectrum of critically ill patients in whom a detrimental effect of etomidate would be most significant clinically, maximizing the signal to noise ratio.

OUTCOMES MEASURED

The primary outcome was the mean difference in the maximum sequential organ failure assessment scores (SOFAs) between groups during the first 3 days in the ICU. Secondary outcomes included the difference between the maximum and admission SOFA scores (Δ -SOFA), mortality, the proportion of patients diagnosed with adrenal insufficiency, the number of ventilator-free days, and ICU length of stay at 28 days.

SAMPLE SIZE CALCULATION

The authors powered the RCT to detect a difference in maximum SOFA scores of 2 points with 80% power at a .05 (two-tailed) significance level for the combined subgroup of sepsis and trauma patients. The minimum required sample size was 130 patients for the subgroup of sepsis and trauma patients, requiring an estimated enrolment of 650 patients.

RESULTS

Of 689 patients assessed for eligibility, 655 were randomized and 650 were analyzed. Of these, 27 died prior to reaching the hospital and 154 were discharged from the ICU within 3 days and therefore excluded from the mITT analysis, leaving 469 patients for analysis. With comparable baseline characteristics between groups, the authors found no statistically significant differences in maximum SOFA and Δ -SOFA scores, mortality, or ventilator- or ICU-free days between groups, although all end points favoured the ketamine-treated group (Table 1). Of the patients meeting the criteria for inclusion in the mITT analysis, 232 were evaluated for adrenal dysfunction based on the discretion of their treating physicians. In this population, there was a statistically significant increase in the proportion of patients diagnosed with adrenal insufficiency in the etomidate-treated group (Table 2).

When looking at the a priori defined subgroup of septic or trauma patients, there were no statistically significant differences in any of the outcomes (Table 3 and Table 4). However, when septic patients were looked at in isolation, the point estimates of mean maximum SOFA scores and mortality, although not meeting the conventional cutoff for statistical significance, indicated harm in patients receiving etomidate (see Table 3).

Table 1. Results from mITT analysis

Outcome	Etomidate (<i>n</i> = 234)	Ketamine (<i>n</i> = 235)	Difference (95% CI)
Maximum SOFA, mean (SD)	10.3 (3.7)	9.6 (3.9)	0.7 (0.0 to 1.4)
Δ -SOFA (median, IQR)	1.5 (0.3)	1.0 (0.3)	0.5 (-1 to 1)
28-day mortality, <i>n</i> (% , 95% CI)	81 (35, 29 to 41)	72 (31, 25 to 37)	4 (-4 to 12)

IQR = interquartile range; mITT = modified intention-to-treat; SOFA = sequential organ failure assessment score.

Table 2. Assessment of adrenal function in patients who were assessed for adrenal dysfunction

Outcome	Etomidate (<i>n</i> = 116)	Ketamine (<i>n</i> = 116)
Baseline cortisol, nmol/L (median [IQR])	441 (304–717)	690 (469–938)
Nonresponse to ACTH stimulation test, % (95% CI)	93 (81, 76–86)	49 (42, 36–48)
Adrenal insufficiency, % (95% CI)	100 (86, 82–90)	56 (48, 42–54)

ACTH = adrenocorticotrophic hormone; IQR = interquartile range.
*The diagnosis of adrenal insufficiency was made if the response to the ACTH stimulation test resulted in a rise in cortisol level of under 250 nmol/L, the baseline cortisol level was under 276 nmol/L, or both.

Table 3. Maximum SOFA scores in septic or trauma patients

	Etomidate	Ketamine	Difference (95% CI)
Septic or trauma patients, mean (SD)	11.0 (3.8, <i>n</i> = 98)	10.3 (3.6, <i>n</i> = 82)	0.7 (0.4 to 1.8)
Septic patients, mean (SD)	12.4 (3.5, <i>n</i> = 41)	10.8 (4.5, <i>n</i> = 35)	1.6 (−0.3 to 3.4)
Trauma patients, mean (SD)	10.0 (3.5, <i>n</i> = 57)	9.9 (2.8, <i>n</i> = 47)	0.1 (−1.2 to 1.3)

SOFA = sequential organ failure assessment score.

Table 4. 28-Day mortality in septic or trauma patients

	Etomidate (% , 95% CI)	Ketamine (% , 95% CI)	Odds Ratio (95% CI)
All patients (<i>N</i> = 469)	81/234 (35, 29–41)	72/235 (31, 25–37)	1.2 (0.8–1.8)
Septic or trauma patients (<i>n</i> = 180)	32/98 (33, 24–42)	26/82 (32, 23–42)	1.0 (0.6–2.0)
Septic patients (<i>n</i> = 76)	17/41 (41, 28–57)	12/35 (34, 21–51)	1.4 (0.5–3.5)
Trauma patients (<i>n</i> = 104)	15/57 (26, 17–39)	14/47 (30, 19–44)	0.8 (0.4–2.0)

STUDY CONCLUSIONS

The authors concluded that a bolus dose of etomidate for RSI was not associated with increased morbidity and mortality compared to ketamine in critically ill patients but suggested that ketamine is a safe alternative.

COMMENTARY

The controversy surrounding etomidate centres primarily around its use in septic patients, in whom observational data suggest that transient adrenal insufficiency may be associated with greater mortality.^{3,4,6–10} Jabre and colleagues did not specifically study septic patients but studied critically ill patients in general and conducted an a priori defined subgroup analysis on a combined subgroup of septic or trauma patients.

By combining septic and trauma patients into one subgroup, the authors may have diluted an existing harmful effect in septic patients, given that the subgroup analysis of trauma patients showed no trend toward harm with etomidate. We are concerned that the point estimate in the most relevant outcome (mortality) favoured ketamine over etomidate in septic patients. However, owing to the small numbers of septic patients, the confidence intervals were wide and did not meet the criteria for statistical significance.

It is important to note that despite a lack of statistical significance, Jabre and colleagues' data indicate that the most precise point estimate for the odds of death after intubation with etomidate is 40% higher than with ketamine.¹¹ Considering this, does a lack of achieved statistical significance in this end point justify a conclusion whereby etomidate is regarded as being as safe as ketamine?

The authors used the SOFA score as a surrogate marker rather than a patient-oriented outcome, such as mortality, as the primary outcome. The SOFA score is a scoring system used to quantify the extent of organ failure and the severity of illness that correlates with in-hospital and ICU mortality.¹² Any time a surrogate end point is used, clinicians must question whether the surrogate marker accurately reflects the clinically relevant outcome measure it is replacing. If the surrogate marker is not sufficiently sensitive for the outcome it is representing, the surrogate marker may fail to detect a difference between groups when one actually exists (a type II error). Despite reported area under the curves varying from fair to good,¹² the actual sensitivity of maximum SOFA scores for mortality at a score of 10 has been reported between 60 and 75%.^{13–15} This means that up to 40% of patients who ultimately die may have maximum SOFA scores below 10, leading us to question the validity of using the maximum SOFA score as a primary outcome measure.

Conversely, had the authors powered their study to detect a difference in mortality, the clinically more significant end point, they would have required a significantly greater sample size. Based on data from their trial, the authors would have had to enrol 4,854 patients to obtain sufficient septic patients to detect a relative mortality difference of 40% between groups (corresponding to an absolute difference of 12%) with 80% power at a .05 significance level. To detect a relative mortality difference of 20%, they would have needed 18,127 patients.

CONCLUSION

We commend the authors on an ambitious and well-conducted RCT. However, because of the limitations in sensitivity of the surrogate end point used, the lack of power to detect a significant difference in mortality in septic patients, and mortality end points favouring ketamine, we are concerned that a significant difference in outcomes for septic patients has not been excluded. The emergency medicine community still waits for the definitive answer on the use of etomidate for intubation in septic patients. In the meantime, the most cautious approach is to avoid the use of etomidate in septic patients.

Competing interests: None declared.

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