# Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial

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## Summary

**Background** Critically ill patients often require emergency intubation. The use of etomidate as the sedative agent in this context has been challenged because it might 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 randomised, 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 computerised 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 analysed 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.

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## Introduction

Critically ill patients often require emergency orotracheal intubation for airway control. Rapid sequence intubation with administration of a sedative and a paralytic agent is common. Etomidate is the sedative-hypnotic drug that is most often used in rapid sequence intubation, but its use has been challenged because it can cause a reversible adrenal insufficiency by dose-dependent inhibition of 11β-hydroxylase.[1,2]

Several studies have suggested an association between the use of etomidate and the occurrence of adrenal insufficiency and increased morbidity in critically ill or injured patients, particularly in those with sepsis.[3–8] Because adrenal insufficiency when a patient is critically ill can increase the risk of death, several investigators have advised against the use of etomidate, even as a single bolus.[9] However, no causal link has been established between its use and an increase in morbidity and mortality.

Etomidate's haemodynamic tolerance, even in patients with shock, and the excellent intubation conditions provided have to be weighed against potential adverse effects, including adrenal insufficiency.[10] A possible alternative to etomidate is ketamine, which is not known to inhibit the adrenal axis. The aim of this randomised controlled study was to compare early and 28-day morbidity after a single dose of etomidate or ketamine used for emergency endotracheal intubation of critically ill patients.

## Methods

### Study setting and patients

This prospective, randomised, controlled, single-blind (caregiver) trial was undertaken from April 25, 2007, to Feb 27, 2008, by 12 emergency medical services or emergency departments and 65 intensive care units in France. The emergency medical services are ambulance base stations equipped with one or more mobile intensive care units, consisting of an ambulance driver, a nurse, and a senior emergency physician as the minimum team.[11]

Patients who were 18 years or older and who needed sedation for emergency intubation were prospectively

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enrolled in the study. Exclusion criteria were cardiac arrest; contraindications to succinylcholine, ketamine, or etomidate; or known pregnancy. As specified in the analysis plan, we excluded, after randomisation, patients who were discharged alive from the intensive care unit within 3 days, to retain only the most severely ill patients. We also excluded after randomisation patients who died before reaching the hospital because their death could not reasonably have been attributed to sedative use. The modified intention-to-treat analysis (mITT population) included all other randomised patients.

The study was approved by Aulnay Hospital's Ethics Committee for the Protection of Persons (number AOM06103). Informed consent was waived at randomisation because patients needed urgent intubation. Whenever a patient was included without written informed consent, such consent was promptly sought, according to the French Law of Ethics, from a legally authorised representative and subsequently from the patient.

## Procedures

Patients were randomly assigned in a 1:1 ratio to either etomidate (Lipuro, B Braun Medical, Boulogne, France) administered as a 0·3 mg/kg intravenous bolus, or to ketamine (Ketalar, Panpharma, Fougères, France) administered as a 2 mg/kg intravenous bolus. Randomisation



*Figure 1:* Trial profile
ICU=intensive care unit.

was done in blocks of four by a computerised random-number generator list provided by a statistician who was not involved in determination of patient eligibility, drug administration, or outcome assessment. In every centre, the study drug was sealed in sequentially numbered, identical boxes containing the entire treatment for each patient. The emergency physician enrolling patients was aware of study group assignment. However, nurses and intensivists in the intensive care unit were masked to the treatment assigned because it was not specified on the patient's medical record or conveyed in verbal or written reports. Additionally, none of the emergency physicians enrolling patients were members of the staff in the intensive care unit, and they had no influence on the management of the patients while they were in intensive care.

Succinylcholine (Celocurine, Orion Pharma, Levallois Perret, France) was given immediately after the sedative as a 1 mg/kg intravenous bolus. After confirmation of intubation and tube placement, continuous sedation was initiated by use of a standardised protocol with midazolam (0·1 mg/kg/h) combined with fentanyl (2–5 μg/kg/h) or sufentanil (0·2–0·5 μg/kg/h).

Organ system function was defined for each of the six major organ systems with the sequential organ failure assessment (SOFA) with a scale ranging from 0 to 4 for each organ system, for an aggregate score of 0–24, with high scores indicating severe organ dysfunction.[12] The Glasgow coma score was recorded immediately before rapid sequence intubation to assess the neurological component of the SOFA at admission. The other components of the SOFA were computed with the worst values recorded for corresponding variables within the preceding 24 h. The maximum SOFA score was defined by the sum of the maximum values for each organ system during the follow-up period.[13] We assessed organ dysfunction and failure occurring after admission to the intensive care unit (Δ-SOFA) by computing the maximum SOFA score minus the admission SOFA score.[14]

We defined adrenal insufficiency as a random cortisol concentration of less than 276 nmol/L or a difference from baseline concentration of less than 250 nmol/L at 30 min or 60 min after adrenocorticotropin hormone stimulation test.[15] A patient was defined as a non-responder if the increase in cortisol did not exceed 250 nmol/L at these times.[16]

We computed the intubation difficulty score—a measure of intubation difficulty—as the sum of seven variables (number of attempts, number of operators, number of alternative techniques, glottic visualisation, lifting force, use of external laryngeal pressure, and vocal cords position).[17] A value greater than 5 (on a scale ranging from 0: easy intubation; to infinity: intubation impossible) is synonymous to difficult intubation.[17]

For the clinical assessment, we recorded general characteristics of the patient including demographics, presenting symptoms, and final diagnoses; severity of
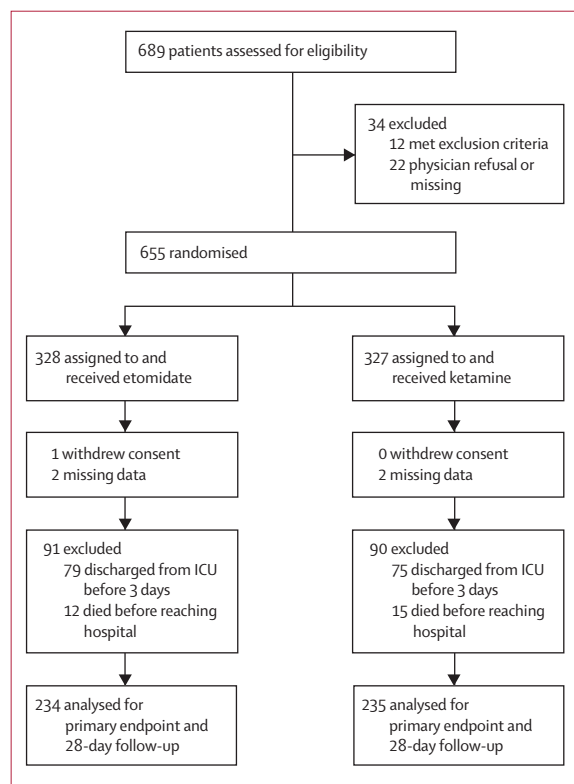
| | Etomidate (n=234) | Ketamine (n=235) |
|---|---|---|
| Age (years) | 57 (18) | 59 (19) |
| Men | 147 (63%) | 133 (57%) |
| Weight (kg) | 75 (18) | 74 (18) |
| **Previous or coexisting conditions** | | |
| Hypertension | 78 (33%) | 79 (34%) |
| Coronary disease | 20 (9%) | 34 (15%) |
| Chronic heart failure | 19 (8%) | 26 (11%) |
| Stroke | 37 (16%) | 40 (17%) |
| COPD | 31 (13%) | 30 (13%) |
| Diabetes | 32 (14%) | 31 (13%) |
| Chronic renal failure | 8 (3%) | 9 (4%) |
| Regular alcohol consumption | 42 (18%) | 40 (17%) |
| HIV | 0 | 4 (2%) |
| Smoking | 46 (20%) | 59 (25%) |
| Cancer | 12 (5%) | 18 (8%) |
| **Activity limitation*** | | |
| A | 142 (61%) | 138 (59%) |
| B | 54 (23%) | 58 (25%) |
| C | 24 (10%) | 29 (12%) |
| D | 11 (5%) | 10 (4%) |
| Missing | 3 (1%) | 0 |
| **McCabe classification†** | | |
| 1 | 160 (68%) | 162 (69%) |
| 2 | 59 (25%) | 55 (23%) |
| 3 | 12 (5%) | 18 (8%) |
| Missing | 3 (1%) | 0 |
| **Reasons for emergency intubation** | | |
| Comatose | 162 (69%) | 162 (69%) |
| Shock | 31 (13%) | 26 (11%) |
| Acute respiratory failure | 37 (16%) | 41 (17%) |
| Other | 4 (2%) | 6 (3%) |
| **Disease severity at inclusion** | | |
| Temperature (°C) | 36·4 (1·6) | 36·4 (1·7) |
| Heart rate (beats/min) | 98 (27) | 97 (29) |
| Systolic blood pressure (mm Hg) | 132 (38) | 128 (32) |
| Diastolic blood pressure (mm Hg) | 78 (23) | 75 (19) |
| $SpO_2$ (%) | 93 (10) | 93 (9) |
| Glasgow coma scale (median [range]) | 6 (3–15) | 7 (3–15) |
| | | (Continues on next column) |

| | Etomidate (n=234) | Ketamine (n=235) |
|---|---|---|
| (Continued from previous column) | | |
| **Laboratory values at admission** | | |
| $PaO_2/FiO_2$ (mm Hg) | 299 (190) | 282 (148) |
| WBC (thousands/mm³) | 14·2 (8·9) | 12·9 (6·2) |
| Haemoglobin (g/L) | 122 (26) | 121 (23) |
| Platelets (thousands/mm³) | 210 (84) | 214 (89) |
| Glucose (mmol/L) | 9 (4) | 9 (5) |
| Arterial lactates (mmol/L) | 3 (3) | 3 (3) |
| SAPS II | 51·2 (18·3) | 50·5 (17·4) |
| **Final diagnosis** | | |
| Trauma | 57 (24%) | 47 (20%) |
| Sepsis | 41 (18%) | 35 (15%) |
| Other | 136 (58%) | 153 (65%) |

Data are mean (SD) or number (%), unless otherwise indicated. COPD=chronic obstructive pulmonary disease. $SpO_2$=pulse oxygen saturation. $PaO_2/FiO_2$=the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. WBC=white blood cells. SAPS=simplified acute physiology score II. *Activity levels were defined as follows (Knaus chronic health status score): A, previous good health, no functional limitations; B, mild to moderate limitation of activity because of a chronic medical problem; C, chronic disease producing serious but not incapacitating limitation of activity; and D, severe restriction of activity due to disease, including people bedridden or institutionalised because of illness. †McCabe classification: 1, non-fatal disease; 2, ultimately fatal disease; and 3, rapidly fatal disease.

*Table 1:* Baseline characteristics of study patients

illness assessed by vital signs, simplified acute physiology score II, and SOFA score; and interventions including transfusions, intravenous fluid volume, administration of vasopressors, and mechanical ventilation during the first 3 days.

For laboratory variables we recorded haematological and chemistry data, and arterial blood gas determinations. When recommended by the physician, a short adrenocorticotropin hormone test was done during the 48 h after admission, with blood samples taken immediately before and 30–60 min after an intravenous bolus of 0·25 mg tetracosactrin (Novartis, Stein, Switzerland).

During the 28-day period after randomisation (follow-up period), we collected data for vital signs, results from laboratory tests, and any major interventions done. We recorded mortality at 28 days and at discharge from intensive care unit. Throughout the study, a Data Safety Monitoring Board monitored patients' safety every 3 months.

The primary endpoint was the maximum SOFA score during the first 3 days in the intensive care unit. The SOFA score during the first few days of admission was chosen because adrenal insufficiency due to etomidate is reversible and lasts up to 48 h,[7] and because it is a reliable prognostic indicator.[13,18] Secondary endpoints were Δ-SOFA score (maximum score minus admission score), 28-day all-cause mortality, days free from intensive care unit, and organ support-free days (mechanical ventilation and vasopressor) during the 28-day follow-up. Safety was assessed by recording serious adverse events and particularly the intubation difficulty score, the absolute difference in arterial blood pressure before and after intubation, oxygen saturation, and cardiac arrest during intubation.

## Statistical analysis

We defined a priori that the combined subgroup of patients with a final diagnosis of confirmed sepsis or trauma was of major clinical interest. The sample size calculation was therefore designed to provide a sufficient power for analysing this subgroup. On the basis of

| | Etomidate (n=234) | Ketamine (n=235) | Difference (95% CI) | p value |
|---|---|---|---|---|
| **Outcomes** | | | | |
| SOFA$_{max}$ score (mean [SD]) | 10·3 (3·7) | 9·6 (3·9) | 0·7 (0·0 to 1·4) | 0·056 |
| Δ-SOFA (median [IQR])* | 1·5 (0 to 3) | 1 (0 to 3) | 0·5 (–1 to 1)† | 0·20 |
| 28-day mortality (n [%, 95% CI]) | 81 (35%, 29 to 41) | 72 (31%, 25 to 37) | 4 (–4 to 12) | 0·36 |
| Mechanical ventilation-free days at day 28 (median [IQR]) | 12 (0 to 25) | 15 (0 to 26) | –2·4 (–9·9 to 5·7)† | 0·36 |
| Transfusions (n [%, 95% CI]) | 42 (18%, 13 to 23) | 38 (16%, 11 to 21) | 2 (–5 to 9) | 0·62 |
| Fluid loading (mL/kg/h; mean [SD]) | 2 (1) | 2 (4) | –0·1 (–0·7 to 0·5) | 0·23 |
| Catecholamine support (n [%, 95% CI]) | 137 (59%, 53 to 65) | 120 (51%, 45 to 57) | 7·5 (–1·5 to 16·5) | 0·10 |
| Catecholamine-free days (until day 28; median [IQR]) | 27 (14 to 28) | 28 (20 to 28) | –0·7 (–2·1 to 0·2)† | 0·08 |
| ICU-free days at day 28 (median [IQR]) | 4 (0 to 22) | 6 (0 to 23) | –2 (–13 to 11)† | 0·57 |
| Glasgow outcome score (median [IQR]) | 3 (1 to 5) | 3 (1 to 5) | 0 (–1 to 1)† | 0·95 |
| **Intubation condition** | | | | |
| IDS value (median [IQR]) | 1 (0 to 3) | 1 (0 to 3) | 0 (0 to 0)† | 0·70 |
| Difficult intubation (n [%, 95% CI])‡ | 24 (10%, 6 to 14) | 20 (9%, 5 to 13) | 2 (–4 to 7) | 0·52 |
| Change in arterial systolic blood pressure (mm Hg; median [IQR])§ | 5 (–11 to 30) | 10 (–10 to 33) | –5 (–13 to 2)† | 0·24 |
| Change in arterial diastolic blood pressure (mm Hg; median [IQR])¶ | 1 (–8 to 13) | 5 (–7 to 18) | –4 (–8 to 1)† | 0·18 |
| Change in SpO$_2$ (%; median [IQR])‖ | 1% (0 to 6) | 2% (0–7) | –1 (–2 to 1)† | 0·98 |
| Cardiac arrest during intubation (n [%]) | 7 (3%) | 4 (2%) | 1·3 (–1·5 to 4·0) | 0·36 |

SOFA$_{max}$=the maximum value of the sequential organ failure assessment (SOFA) score during the first 3 days in intensive care. ICU=intensive care unit. IDS=intubation difficulty score. SpO$_2$=pulse oxygen saturation. *Δ-SOFA= SOFA$_{max}$-SOFA(admission). †Bootstrap CI for median difference. ‡Difficult intubation is defined as IDS>5. §Change in arterial systolic blood pressure equals pre-intubation minus post-intubation arterial systolic blood pressure. ¶Change in arterial diastolic blood pressure equals pre-intubation minus post-intubation arterial diastolic blood pressure. ‖Change in SpO$_2$ equals post-intubation minus pre-intubation SpO$_2$.

*Table 2:* **Primary and secondary endpoints and intubation condition for study patients**

Moreno and colleagues' study,[14] the relevant difference in maximum SOFA score to be detected between the two treatment groups was considered equal to 2 points. With an SD of 4,[14] a sample size of 130 patients allowed an 80% power to detect this difference with a two-sided t test with type-I error of 0·05. Since we analysed the mITT population for the primary analysis (ie, we excluded from the analysis randomised patients who died before reaching hospital and those discharged from the intensive care unit within 3 days), and we anticipated that about 30% of patients would die before reaching hospital or be discharged alive before 3 days, we determined that 200 patients should be included in the subgroup of interest, allowing for about 5% of patients with important data missing. After considering that this subgroup would account for about 30% of the total randomised population, we decided to recruit a total population of 650 patients.

Results are given as mean (SD) for normally distributed variables, as medians (IQR) for non Gaussian quantitative variables, and as numbers and percentages (95% CI) for categorical variables. After checking normality of the distribution, we compared the maximum SOFA scores in the two groups with generalised linear models adjusted for centre (including a group×centre interaction in the models). Since we excluded patients for the mITT analysis and had thus possibly interfered with the randomisation, we decided a posteriori to make a complementary sensitivity analysis adjusted for age, simplified acute physiology score II, and sex.

For secondary endpoints, the two groups were compared by student's t test or Wilcoxon rank-sum test for normally or non-normally distributed quantitative variables, respectively. We compared categorical data with either the χ² or Fisher's exact test, as appropriate. Odds ratios for death and their 95% CI were estimated in the mITT population and in the predefined subgroups. Time to event within the 28-day follow-up of the study was described by survival curves with Kaplan-Meier's method, and the hazard ratio with 95% CI was estimated between the two groups. Patients who died during the follow-up period before being weaned from catecholamine support or mechanical ventilation were regarded as not having been weaned within the 28-day follow-up.

All statistical tests were two-sided. The chosen type-1 error rate was a p value less than 0·05, except when testing the subgroup of patients with sepsis or trauma for which a Bonferroni's adjustment for multiplicity was used (p<0·025). Analyses were done with SAS statistical software (version 9.1.3).

This trial is registered with ClinicalTrials.gov, number NCT00440102.

### Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing the report. All authors had full access to all the data in the study, and all agreed to submit for publication.

## Results

Figure 1 shows the trial profile. Of the 689 patients assessed for eligibility, 655 were consecutively and randomly assigned to treatment and 650 were analysed (ITT population; figure 1). All allocated treatments were delivered to the randomised patients. The mITT analysis was undertaken in 469 patients (n=234 in etomidate group and n=235 in ketamine group). The number of patients who died before reaching hospital or who were discharged alive before 3 days from the intensive care unit was similar in the two groups (figure 1).

Baseline characteristics of the patients were similar in both groups (table 1). Coma was the main reason for intubation. Trauma was the final diagnosis in 104 (22%) patients and sepsis in 76 (16%) (table 1). Other diagnoses included stroke (50 patients in etomidate group vs 54 in ketamine group), drug poisoning (41 vs 51), cardiogenic shock (21 vs 28), acute respiratory failure (19 vs 15), or various others (five vs five).

The maximum SOFA score did not differ significantly between the two groups (table 2). We did not record any centre effect (p=0·30) nor interaction between the primary endpoint and centre (p=0·78). The Δ-SOFA score from maximum to admission did not differ significantly between the two groups (table 2). Furthermore, none of the six components of the SOFA score differed significantly between the etomidate and the ketamine groups (data not shown). In the sensitivity analysis adjusted for age, simplified acute physiology score II, and sex, the difference between the two groups remained non-significant (0·6 [95% CI 0·0–1·3]; p=0·064).

We detected no statistical difference between the two groups in secondary outcome measures—ie, in difficulty of intubation or in early complications after intubation (table 2). Furthermore, 28-day mortality, catecholamine-free days at day 28, duration of catecholamine weaning, percentage of patients needing catecholamine, mechanical ventilation-free days at day 28, duration of weaning from the ventilator, and length of stay in the intensive care unit did not differ between groups (table 2 and figure 2). We recorded no serious adverse events with either study drug. In an ITT analysis including 650 patients, we recorded no significant difference between the two groups for either maximum SOFA score or 28-day mortality (mean difference 0·4 [95% CI –0·2 to 1·0], p=0·20; and 2% [–6 to 10], p=0·54, respectively).

We assessed adrenal axis function in 232 patients (116 per group). Basal cortisol was significantly lower in the etomidate group, and the percentage of non-responders to the adrenocorticotropin hormone stimulation test was significantly higher than in the ketamine group (OR 5·8 [95% CI 3·2–10·5]; table 3). 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; table 3). Mortality did not differ significantly between non-responders and responders (44/142 [31%, 95% CI 23–39] vs 19/90 [21%, 13–29]; p=0·11).
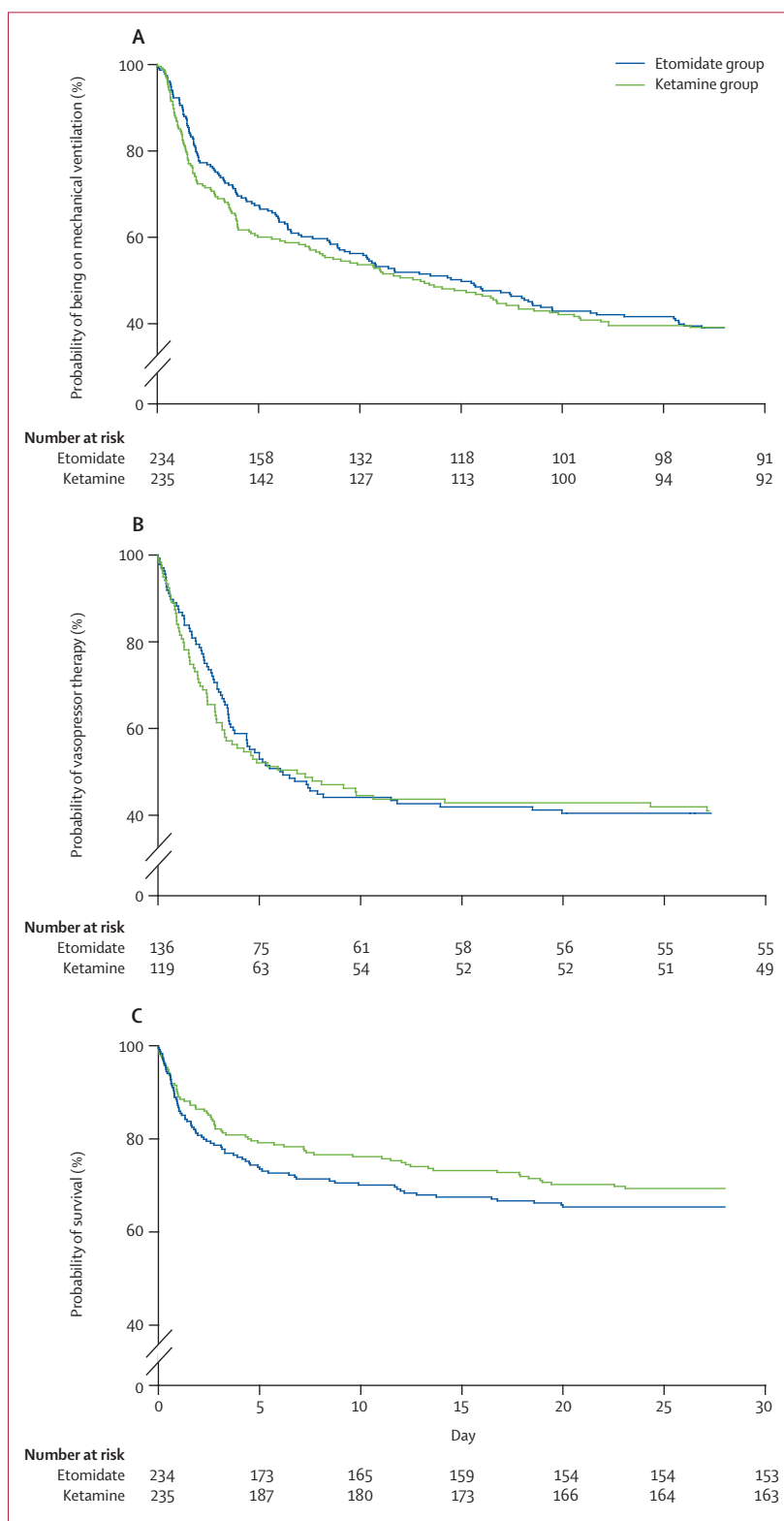


*Figure 2*: **Kaplan-Meier curves comparing patients receiving etomidate or ketamine for emergency intubation**
(A) Time to mechanical ventilation weaning. (B) Time to vasopressor weaning (etomidate group, n=136; ketamine group, n=119). (C) Survival from randomisation to day 28 (hazard ratio 1·2, 95% CI 0·9–1·6).

|  | Etomidate (n=116) | Ketamine (n=116) | p value |
|---|---|---|---|
| Cortisol (nmol/L; median [IQR]) | | | |
| Baseline | 441 (304–717) | 690 (469–938) | <0·0001 |
| 30 min after ACTH test | 497 (331–800) | 911 (690–1131) | <0·0001 |
| 60 min after ACTH test | 524 (386–828) | 1048 (776–1324) | <0·0001 |
| Non-responder in ACTH test (n [%, 95% CI])* | 93 (81%, 76–86) | 49 (42%, 36–48) | <0·0001 |
| Adrenal insufficiency (n [%, 95% CI]) | 100 (86%, 82–90) | 56 (48%, 42–54) | <0·0001 |

ACTH=adrenocorticotropin hormone. *Patient was a non-responder if maximum change was less than 250 nmol/L. †Patient had adrenal insufficiency if baseline cortisol was less than 276 nmol/L or the maximum change (peak cortisol minus baseline cortisol) was less than 250 nmol/L, or both.

*Table 3:* **Adrenal function assessment in study patients†**
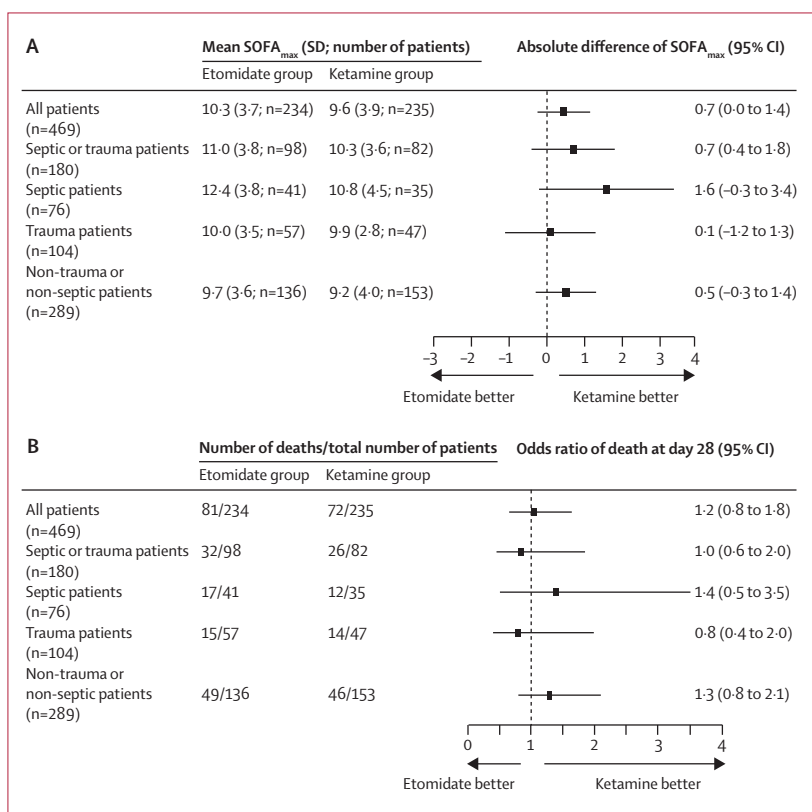


*Figure 3:* **Outcomes of patients receiving etomidate or ketamine for emergency intubation according to subgroups**
(A) Absolute difference in maximum score on the sequential organ failure assessment (SOFAmax). (B) Death within 28 days.

We recorded no significant differences in maximum SOFA score nor mortality between the etomidate and ketamine recipients in the subgroup analysis, which included patients with trauma or sepsis (n=180), sepsis patients only (n=76), trauma patients only (n=104), or patients with neither sepsis nor trauma (n=289; figure 3).

## Discussion

Our study shows that one etomidate bolus is not associated with a significant increase in morbidity or mortality compared with ketamine in patients admitted to the intensive care unit. The maximum SOFA score did not differ significantly between the two drugs in the subgroup of patients having sepsis or trauma. However, for the subgroup of septic patients (n=76), the small number of patients might account for the absence of significant difference. The mortality rate at day 28 in this subgroup did not differ between the treatment groups.

An association between the administration of etomidate and an increased mortality of patients with sepsis has been suggested previously. In a retrospective study of children with meningococcal sepsis or shock,[7] mortality rate was 30% in patients who received etomidate versus 12% in those who did not, but the difference was not significant (OR 3·1 [95% CI 0·3–79·3]). In a post-hoc analysis of the Corticus study undertaken in patients with severe sepsis,[16] the 28-day mortality rate was significantly higher in patients who received etomidate than in those who did not (p=0·03). The investigators, however, did not draw any cause and effect conclusion, presumably because of the lack of randomisation to sedative agents.

By contrast with the substantial increase in mortality reported by Ledingham and Watts,[3] etomidate did not affect outcome in trauma patients in our study. This discrepancy between the two studies is probably related to the duration of etomidate administration: one bolus in our study versus prolonged sedation in Ledingham and Watts' study. Hildreth and co-workers[8] reported increased use of blood products, ventilator days, and days in intensive care in trauma patients randomly assigned to etomidate (n=18) versus midazolam (n=12), but reported no difference in mortality. However, interpretation of this study is difficult because half of the eligible patients were excluded, with 11 of 31 patients having received etomidate.

Although adrenal axis dysfunction arises to some extent after etomidate use for rapid sequence intubation, the effect of such adrenal suppression on patients' outcome remains debated. Studies have reported increased mortality in non-responders to the adrenocorticotropin hormone stimulation test and in patients with adrenal insufficiency.[4,5] One bolus of etomidate decreases cortisol secretion, which contributed to the increased morbidity and mortality reported in several studies.[6,7,16] However, these findings have not been confirmed by other investigators.[19,20] Clearly, the results of these studies could be biased owing to the presence of multiple confounding factors.

Our study confirms the finding of others that etomidate affects the adrenal axis: according to our criteria, more than four-fifths of etomidate recipients had adrenal insufficiency and were non-responders to the adrenocorticotropin hormone stimulation test. About half of patients given ketamine also had adrenal insufficiency, which emphasises that critical illness per se affects adrenal function. In one study, more than 30% of non-responders had not been exposed to

etomidate,[2] and in another,[21] 51% of patients with septic shock who had not received etomidate were non-responders. Indeed, multiple mechanisms could account for adrenal insufficiency in critically ill patients.[22] Adrenal insufficiency is probably associated with increased mortality in critically ill patients, including those with sepsis; however, whether the adrenal axis suppression and mortality are the result of some underlying process, or whether the adrenal axis suppression causes death, has never been established. Among established independent predictors of low cortisol response to adrenocorticotropin hormone stimulation are a low pH or bicarbonate and platelet count, disease severity, and organ failure.[23] Fentanyl or sufentanil infusion can also modify cortisol concentrations.[24,25] However, these factors should not affect the results of our study since both patient groups received the same type of continuous sedation (fentanyl or sufentanil combined with midazolam).

Etomidate is the sedative-hypnotic drug most often used by emergency physicians for rapid sequence intubation, and is the drug of choice for patients who are haemodynamically unstable.[26] Use of ketamine instead of etomidate might have drawn attention to potential adverse effects of the use of ketamine during the intubation procedure.[10] The most common side-effects of ketamine are psychodysleptic effects, but they could not be observed because, unlike in an operating theatre, patients are not awakened until several hours after intubation. We noted no difference between the sedative drugs tested in our study on the ease of intubation, probably because intubation conditions depend mostly on the muscle relaxant effects of succinylcholine. Accordingly, Sivilotti and Ducharme[27] reported no significant difference in the overall successful intubation in a comparison of three hypnotic drugs.

With regard to the strengths and limitations of our study, we have confirmed the appropriateness of the choice of the maximum SOFA score as the primary endpoint. There is an established relation between the maximum SOFA score and Δ-SOFA score (from maximum to admission) and mortality in patients who are critically ill.[13] Moreover, measurement of the SOFA score has good reliability and accuracy among intensivists.[28] These scores have shown its usefulness in the assessment of in-hospital morbidity in seriously ill patients.[13,29,30]

However, our study might not have had sufficient power to show a significant increase in morbidity related to the use of etomidate in patients with sepsis. Our failure to enrol and analyse a larger number of patients with sepsis could have led to a type-II error for this group. A future study should be based on patients with sepsis only, since the controversy regarding the use of etomidate focuses on these patients. We felt that patients admitted with trauma were important to study as well because of suggestions from recent reports that etomidate might be harmful to this group of patients.[8] In conclusion, our results show that ketamine is a safe and valuable alternative to etomidate for intubation in critically ill patients, particularly in septic patients.

**References**
1 de Jong FH, Mallios C, Jansen C, Scheck PA, Lamberts SW. Etomidate suppresses adrenocortical function by inhibition of 11 beta-hydroxylation. *J Clin Endocrinol Metab* 1984; **59:** 1143–47.
2 Malerba G, Romano-Girard F, Cravoisy A, et al. Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. *Intensive Care Med* 2005; **31:** 388–92.
3 Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet* 1983; **321:** 1270.
4 Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000; **283:** 1038–45.
5 de Jong MF, Beishuizen A, Spijkstra JJ, Groeneveld AB. Relative adrenal insufficiency as a predictor of disease severity, mortality, and beneficial effects of corticosteroid treatment in septic shock. *Crit Care Med* 2007; **35:** 1896–903.
6 Lipiner-Friedman D, Sprung CL, Laterre PF, et al. Adrenal function in sepsis: the retrospective Corticus cohort study. *Crit Care Med* 2007; **35:** 1012–18.
7 den Brinker M, Hokken-Koelega AC, Hazelzet JA, de Jong FH, Hop WC, Joosten KF. One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis. *Intensive Care Med* 2008; **34:** 163–68.
8 Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. *J Trauma* 2008; **65:** 573–79.
9 Annane D. ICU physicians should abandon the use of etomidate! *Intensive Care Med* 2005; **31:** 325–26.
10 Zed PJ, Abu-Laban RB, Harrison DW. Intubating conditions and hemodynamic effects of etomidate for rapid sequence intubation in the emergency department: an observational cohort study. *Acad Emerg Med* 2006; **13:** 378–83.

11  Adnet F, Lapostolle F. International EMS systems: France. *Resuscitation* 2004; **63:** 7–9.

12  Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/ failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22:** 707–10.

13  Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; **286:** 1754–58.

14  Moreno R, Vincent JL, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. *Intensive Care Med* 1999; **25:** 686–96.

15  Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; **36:** 1937–49.

16  Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358:** 111–24.

17  Adnet F, Borron SW, Racine SX, et al. The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997; **87:** 1290–97.

18  Patila T, Kukkonen S, Vento A, Pettila V, Suojaranta-Ylinen R. Relation of the Sequential Organ Failure Assessment score to morbidity and mortality after cardiac surgery. *Ann Thorac Surg* 2006; **82:** 2072–78.

19  Riche FC, Boutron CM, Valleur P, et al. Adrenal response in patients with septic shock of abdominal origin: relationship to survival. *Intensive Care Med* 2007; **33:** 1761–66.

20  Ray DC, McKeown DW. Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. *Crit Care* 2007; **11:** R56.

21  Mohammad Z, Afessa B, Finkielman JD. The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate. *Crit Care* 2006; **10:** R105.

22  Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; **348:** 727–34.

23  de Jong MF, Beishuizen A, Spijkstra JJ, et al. Predicting a low cortisol response to adrenocorticotrophic hormone in the critically ill: a retrospective cohort study. *Crit Care* 2007; **11:** R61.

24  Oltmanns KM, Fehm HL, Peters A. Chronic fentanyl application induces adrenocortical insufficiency. *J Intern Med* 2005; **257:** 478–80.

25  Verborgh C, De Coster R, D'Haese J, Camu F, Meert TF. Effects of chlordiazepoxide on opioid-induced antinociception and respiratory depression in restrained rats. *Pharmacol Biochem Behav* 1998; **59:** 663–70.

26  Sivilotti ML, Filbin MR, Murray HE, Slasor P, Walls RM. Does the sedative agent facilitate emergency rapid sequence intubation? *Acad Emerg Med* 2003; **10:** 612–20.

27  Sivilotti ML, Ducharme J. Randomized, double-blind study on sedatives and hemodynamics during rapid-sequence intubation in the emergency department: The SHRED Study. *Ann Emerg Med* 1998; **31:** 313–24.

28  Arts DG, de Keizer NF, Vroom MB, de Jonge E. Reliability and accuracy of Sequential Organ Failure Assessment (SOFA) scoring. *Crit Care Med* 2005; **33:** 1988–93.

29  Antonelli M, Moreno R, Vincent JL, et al. Application of SOFA score to trauma patients. Sequential Organ Failure Assessment. *Intensive Care Med* 1999; **25:** 389–94.

30  Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; **26:** 1793–800.