Best pharmacological practice in prehospital intubation

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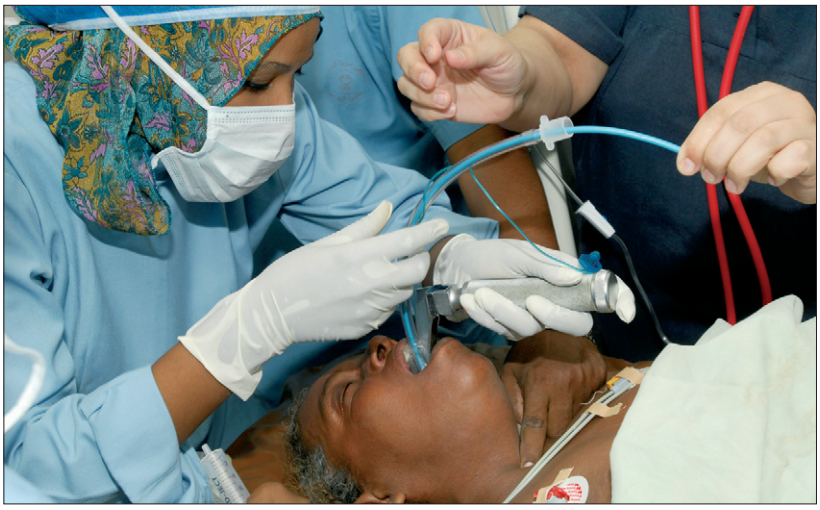
Emergency intubation outside hospital can increase morbidity and mortality[1] because of a lack of careful pre-oxygenation,[2] inadvertent oesophageal intubation,[3] or hypoxic episodes after endotracheal intubation.[4] A Cochrane review last year of 452 studies of a range of cases, providers, and techniques assessing emergency intubation reported that "the efficacy of emergency intubation as currently practised has not been rigorously studied", and that "the skill level of the operator may be key in determining efficacy".[5] The greatest focus when discussing emergency intubation has been on infrequently used and therefore insufficient manual skills and clinical experience of providers undertaking prehospital intubation,[6] resulting in fatal complications when the airway cannot be secured. The Association of Anaesthetists of Great Britain and Ireland[7] states that health-care personnel providing prehospital anaesthesia "should have the same level of training and competence that would enable them to provide unsupervised rapid sequence induction in the emergency department"—namely, a minimum of 2 years of training in emergency specialties and at least 1 year in anaesthesia. However, have pharmacological issues been sufficiently discussed?

In *The Lancet* today, Patricia Jabre and colleagues[8] show that in critically ill patients one dose of 0·3 mg/kg etomidate to ease emergency intubation can result in adrenal axis dysfunction compared with 2 mg/kg ketamine. In this trial, 655 unconscious prehospital patients requiring emergency airway management, because of trauma, sepsis, stroke, drug poisoning, cardiogenic shock, acute respiratory failure, or various other reasons, were randomly assigned, with 469 patients analysed for the primary endpoint: sequential organ failure assessment score during the first 3 days in hospital. Similar prehospital intubation conditions were achieved with both etomidate and ketamine, but only 48% of patients given ketamine had adrenal insufficiency compared with 86% when etomidate was used.

Although Wagner and colleagues[9] described etomidate-mediated adrenal axis dysfunction 25 years ago in a case series, and Malerba and co-workers[10] more recently in intensive care, such dysfunction has now been confirmed in this large, prehospital, randomised trial. In view of today's data, we might have to consider whether successful emergency intubation of critically ill patients depends not only on manual skills and clinical experience but also on pharmacological knowledge. Thus, when caring for acutely ill patients, emergency medical service personnel have to anticipate management in the intensive care unit, and intensive care unit personnel have to consider emergency treatment.

Accomplishment of today's study is a major achievement because neither etomidate nor ketamine are protected by patent, so the drug industry provided no support. The governmental support programme in France for such studies is a role model that enables important non-commercial medical research. Additionally, obtaining informed consent from unconscious patients undergoing emergency interventions is a complex challenge to overcome. Furthermore, following up pathophysiology in hospital that was induced by a prehospital intervention is a major success, since government regulations often block data transfer between emergency medical service providers and hospitals.

The biggest challenge that Jabre and co-workers overcame was increased regulation posed by the European Union, which applies identical requirements for clinical trials irrespective of whether a global pharmaceutical company or a group of academics are investigating a drug. In our experience, these regulations have resulted in a 75% decrease in patients who can be enrolled in a clinical trial with a comparable budget within the past 10 years.[11,12] These obstacles are partly why clinical research in anaesthesia in the UK has fallen by 50% over 10 years.[13] Similarly, investigator-initiated trial



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applications with institutional review boards have sharply decreased in Germany.[14] Although the guidelines for good clinical practice are not proven to prevent publication bias or scientific fraud, or to increase patients' safety or professional conduct of studies, they pose an excessive bureaucratic burden, especially on academic researchers—a heavy toll for rules that were derived on expert consensus only.[14] Today, such consensus would be unacceptable to change clinical guidelines, for which randomised trials yielding statistically significant results are the gold standard for altering recommendations. Disturbingly, the authors of the guidelines for good clinical practice have not been publicly revealed except for the fact that no academic scientists were involved,[15] suggesting that a narrow coalition of industry lobbyists and politicians has created rules that negatively affect health care.

We should be lobbying our parliamentary representatives to help with non-commercial research, otherwise industry lobbyists will continue pushing for rules that only global drug companies can comply with. Should that occur, our fate would be similar to physicians in developing countries, who have many questions about optimising health care but cannot do clinical trials to find valid answers.

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We declare that we have no conflicts of interest.

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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 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.

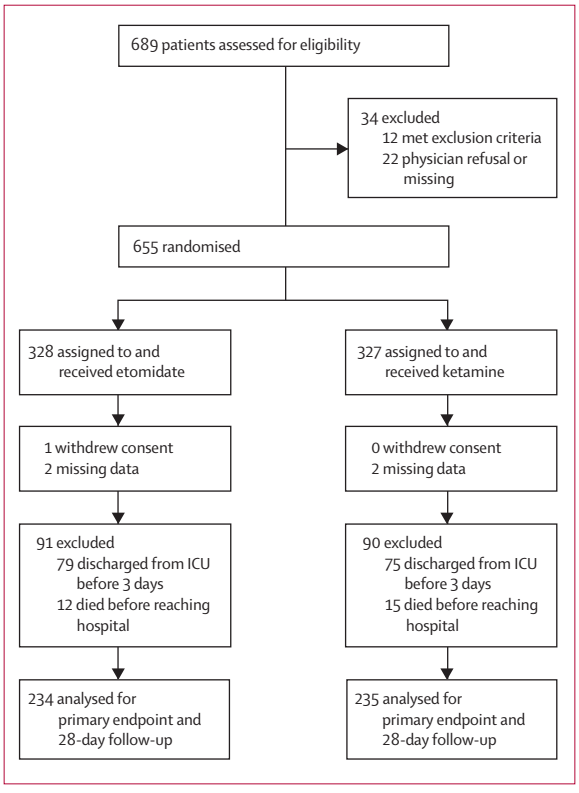

Figure 1: **Trial profile**
ICU=intensive care unit.

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)
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(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 χ^2 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).

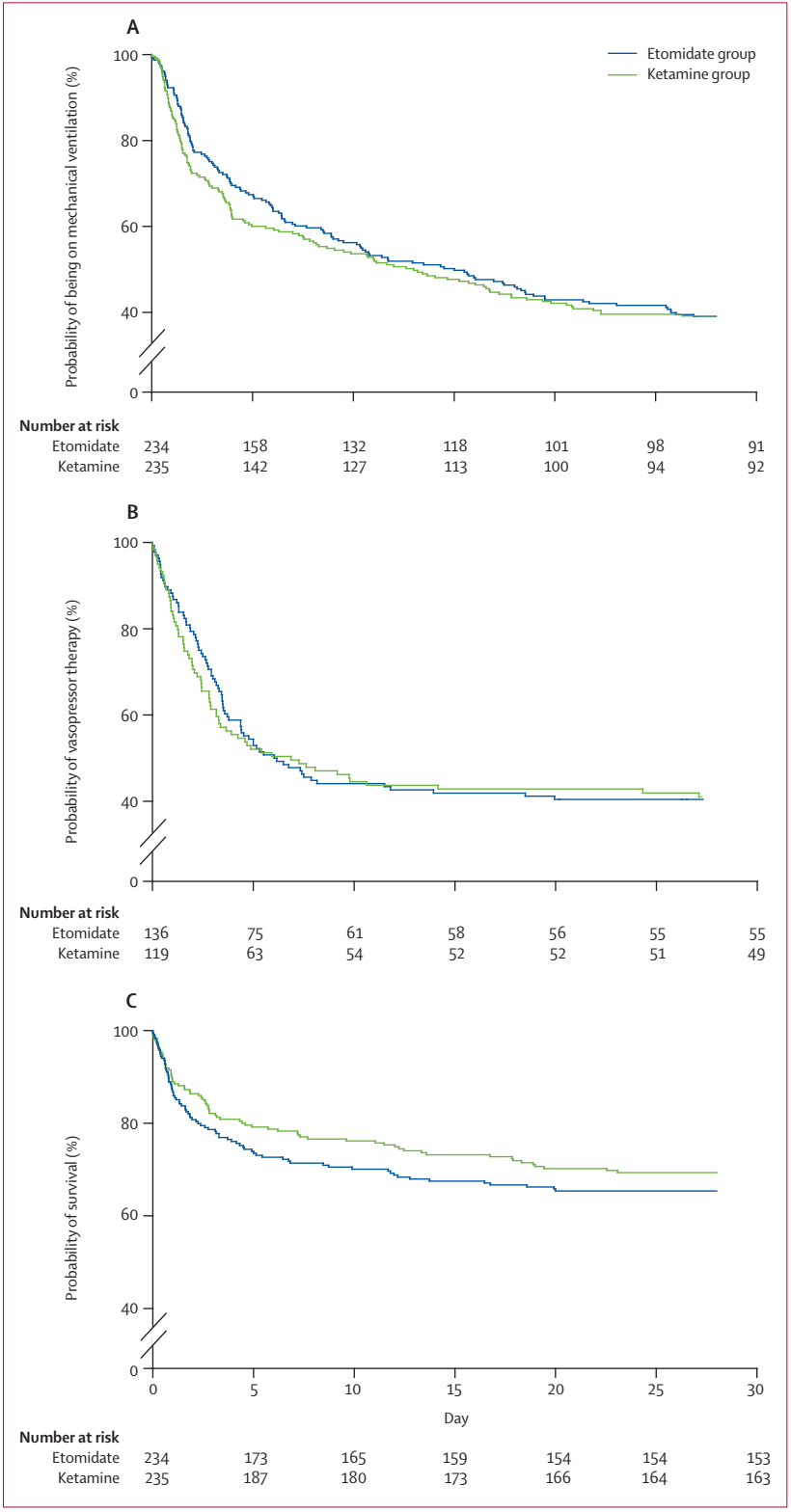

***Figure 2*: Kaplan-Meier curves comparing patients receiving etomidate or ketamine for emergency intubation**

(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†**

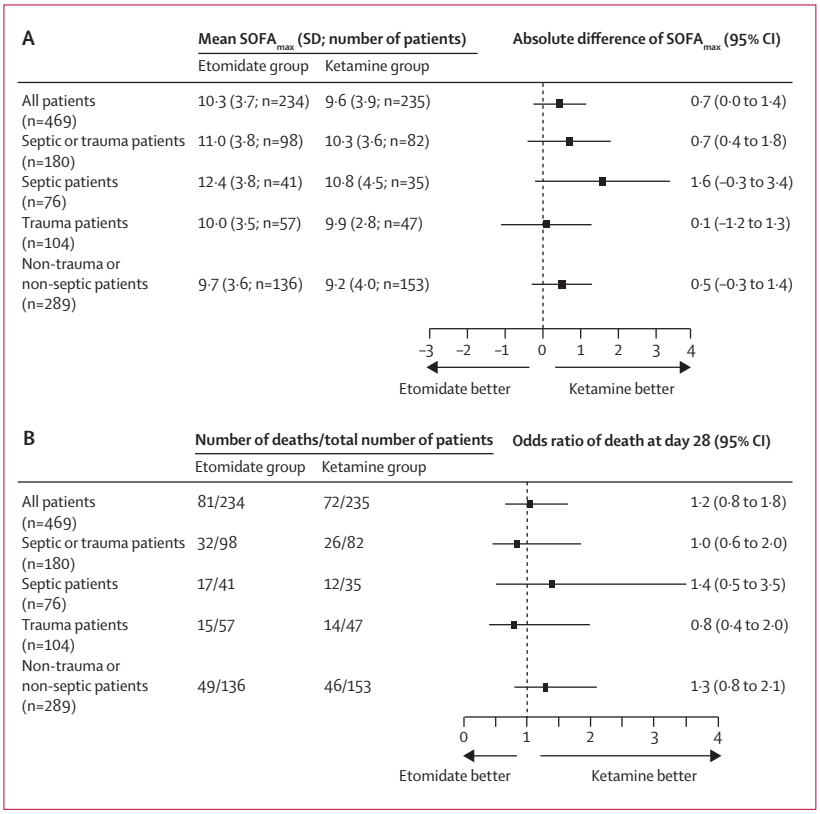

***Figure 3:* Outcomes of patients receiving etomidate or ketamine for emergency intubation according to subgroups**

(A) Absolute difference in maximum score on the sequential organ failure assessment (SOFA$_{max}$). (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

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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.

Contributors

PJ, EV, and FA were responsible for the conception and design of the study. FA obtained funds from the French Ministry of Health to undertake the study. EV and PJ were responsible for data management and statistical analysis. XC, FL, MD, ARH, BV, LB, AB, PG, SA, DP, GL, CCX, VM, and NA participated in the study management, data collection, and interpretation of data. CBB, JYL, PEB, BM, and JDR participated in the study design, interpretation of data, and/or writing of the report. All authors approved the final version of the report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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