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Etomidate and S-ketamine for the intubation of patients on the intensive care unit: a prospective, open-label study

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Abstract

Objective: We compared the mortality rate in patients administered a single dose of etomidate or S-ketamine for tracheal intubation during their stay on the intensive care unit.

Methods: A single centre prospective open-label study was performed. Intensive care patients with a diversity of diagnoses were included. For tracheal intubation, etomidate or S-ketamine were used; the primary endpoint was 28-day mortality. Length of stay, the usage of norepinephrine, and cortisol concentrations were secondary end points.

Results: A total of 322 patients with a mixture of diagnoses were initially included. After exclusions, 301 patients participated; 161 patients in the etomidate group and 140 patients in the S-ketamine group were analysed. The 28-day mortality of the etomidate patients was 38% and of the S-ketamine patients 39% ($p=0.998$). The length of stay was 16 days in the etomidate group and 19 days ($p=0.318$) in the S-ketamine group; the time of norepinephrine administration was 26 versus 29 hours ($p=0.389$) respectively. 24 and 48 hrs after administration of either drug, the cortisol levels had significantly decreased; there was no statistical difference between the etomidate and S-ketamine patients.

Conclusion: In contrast with a currently held opinion, the present study showed that the 28-day mortality after a single dose of etomidate or S-ketamine, administered to patients for tracheal intubation while on the intensive care did not differ.

Introduction

Infusion of etomidate in critically ill patients causes suppression of the cortisol production, which leads to an increase in mortality.¹⁻³ Because of this, etomidate is no longer used for continuous sedation. However, despite the fact that a single dose of etomidate suppresses the cortisol

production for up to 48 hours, etomidate is still used as an induction agent because of its hemodynamic stability.⁴⁻⁶ It remains unclear, however, if this has clinical consequences, despite the fact that several analyses have rejected etomidate as an induction agent.^{7,8} These reviews have to a large extent been based on retrospective studies in septic patients. In two prospective studies, in which etomidate was administered just before admission to the intensive care department, mortality was similar when compared with ketamine or midazolam.^{9,10} However, an induction agent is not only used at the start of critical illness, but also during the subsequent stay in the intensive care. In this situation, the patient's condition can be quite different both with respect to the course of illness and the administration of several other drugs. We initiated a prospective study to compare the mortality in patients after either a single dose of etomidate or a single dose of S-ketamine administered on the ICU at any point during their stay.

Methods

Tracheal intubation in the intensive care is an emergency procedure, for which both etomidate and S-ketamine are registered drugs. As etomidate and S-ketamine were routinely used in our ICU, and because endotracheal intubation of intensive care patients is usually an emergency procedure, the Medical Ethics Committee approved the study with a waiver of informed consent (METC number 11-N-94).

The study was performed in a mixed, surgical and medical, adult ICU with 21 beds in a large teaching hospital from April 2008 until the end of 2009. The ICU consists of three equivalent units, staffed by the same medical staff. These units are not specialized and there is no difference in categories of patients. Etomidate and S-ketamine were common induction agents in all three ICUs. For the first ten months, etomidate (Etomidat®

Lipuro, Braun, Melsungen, Germany) was the induction agent in two units, and S-ketamine (Ketanest-S®, Pfizer, Capelle a/d IJssel, the Netherlands) in the other unit. After ten months the agents were reversed. The medical staff was not involved in patient allocation to a particular unit. Nursing staff, responsible for patient allocation and not involved in the study, decided in which unit the patient would be admitted. Consequently, this is a cluster-randomized trial in which the chosen intensive care unit is the randomized element. All critically ill adult patients, who were intubated in one of the intensive care units, either shortly after admission or during their period of stay, were enrolled in the study. Patients with cerebral pathology were not excluded, because ketamine is deemed safe in these patients.¹¹⁻¹³ Patients, who were already intubated before admission, did not participate; patients who had received etomidate less than 72 hours before were excluded. Etomidate was administered in a dose of 0.2-0.3 mg/kg⁻¹ bodyweight, and S-ketamine 0.5 mg/kg⁻¹. In order to avoid unwanted psychological reactions, midazolam (Midazolam®, Actavis, Hafnarfjörður, Iceland) 2.5 mg, was added to the S-ketamine. For neuromuscular blocking, rocuronium (Rocuroniumbromide®, Fresenius Kabi, Hertogenbosch, the Netherlands) was used; the use of opioids was left to the discretion of the attending intensivist. Corticosteroids were prescribed when necessary as clinical therapy and were not part of the study.

The primary end point was the mortality within 28 days after the administration of etomidate or S-ketamine. The patients were followed for 28 days, also if they were discharged from the intensive care during this period. Secondary outcomes were the length of stay (LOS) in the intensive care unit, and the use of norepinephrine during the first 72 hours after administration of one of the study drugs. Immediately after intubation, and 24 and 48 hours later (t=0, t=24 hours, t=48 hours), blood was taken to determine the cortisol levels. The serum cortisol levels were determined by competitive immunoassay using a commercial kit (Advia Centaur, Siemens AG, Erlangen, Germany).

Table 1. Patient characteristics.

	Etomidate (n=161)	S-ketamine (n=140)	P
Age, years			
mean (sd)	66 (14)	67 (13)	0.523
Male/female	95/66	89/51	0.478
APACHE II			
Mean (sd)	25 (7)	24 (7)	0.224
Diagnosis			
Sepsis	58	54	
COPD	13	14	0.858
Cardiac failure	25	15	
Other	65	57	
Steroid patients*	59	61	0.269

*Patients treated with corticosteroids as clinical therapy

Statistical analysis

Prior to this study, the average mortality rate of mechanically ventilated patients on our intensive care unit was 35%. To exclude a 15% worse outcome in the etomidate patients with a one-sided α risk of 0.05 and power of 90%, at least 106 patients had to be included in each group. Mortality and other categorical data were compared with the Chi-square test. For age, APACHE score, cortisol levels, use of norepinephrine, and LOS the Student's t-test was used.

Results

In total 322 patients were included. After exclusion of the patients who had received etomidate less than 72 hours before, a total of 301 patients – 161 receiving etomidate, and 140 receiving S-ketamine were included. Patient characteristics are presented in table 1, the outcomes in table 2. With respect to the characteristics, the groups were comparable, as were the number of patients treated with corticosteroids. The 28-day mortality did not differ between the groups, neither did the duration of norepinephrine support; also the LOS in the intensive care did not differ. In both the etomidate and in the S-ketamine patients, the cortisol levels at t=24 and t=48 hours had decreased significantly, but did not differ between the groups.

Discussion

In this study, the 28-day mortality was the same after a single dose of etomidate or S-ketamine, administered in one of the ICUs. This result is contrary to the findings that a single dose of etomidate increases mortality, based on retrospective analyses of septic patient populations.¹⁴⁻¹⁶ In these retrospective studies, the use of etomidate was not randomized, and it is possible that, because of its hemodynamic stability, etomidate was just chosen for the most critically ill patients, resulting in a bias.^{7,17} In two prospective studies, comparing etomidate with ketamine or midazolam, mortality was found to be equal.^{9,10} Though Jabre's study⁹ was performed in a series of patients with various diagnoses, patients were intubated outside the intensive care, before admission, while in the present study patients who had been intubated before admission to the ICU were excluded. Furthermore, in the present study, patients were included when intubation took place at any point during their stay on the ICU; therefore, the patients studied in our study are more likely to represent a cross-section of a general ICU adult population.

The equivalence of the secondary end points, LOS and treatment with norepinephrine, could mean that adrenal suppression is the same in both groups of patients, and indeed the cortisol results did not differ. Based on the reports that a single dose of etomidate suppresses cortisol production for up to 48 hours, blood samples were taken at intubation, and at 24 and 48 hours later. Diurnal cortisol rhythm was therefore

not taken into account. However, a diurnal rhythm seems to be absent in critically ill patients with different diagnoses, especially those with a longer stay.¹⁸ The cortisol levels were only included if all three measurements, at t=0, t=24 and t=48 hours, were performed. All three measurements of cortisol were performed in somewhat fewer than half the patients, due to the stir of daily clinical practice. This restricted inclusion means that the results from the patients who died within 48 hours were also omitted. The cortisol levels declined significantly in both groups. Exclusion of the cortisol results, if the set of three was not complete, could create doubts about the conclusion. Still, inclusion of all the cortisol results (not presented) led to the same result.

Although the decrease in cortisol levels after a single dose of etomidate is well known, the cortisol levels also decreased after S-ketamine. A negative influence on the adrenal function, caused by hypnotics other than etomidate, has previously been reported by Jabre et al.⁹ It was demonstrated that after a single dose of ketamine the reaction on the ACTH stimulation test is insufficient in 48% of patients. Sedation of critically ill patients with propofol or midazolam demonstrated a decrease in the cortisol level, although the response to the ACTH test was adequate.¹⁹ And an induction dose of thiopental reduced the response in the ACTH test in 29% of critically ill patients.²⁰ It seems reasonable to conclude that the cortisol reduction found in these studies, and the reduction in both groups of the present study are probably the consequence of the critical illness and the induction of anaesthesia.

The mortality difference of 15%, which was the starting point of the study, can be criticized as a limitation. Although a 15% difference is important, a smaller difference would have been more relevant. However, in order to study this smaller difference a multicentre study will be necessary.

A number of patients were treated with corticosteroids and these therapeutic steroids can influence cortisol measurements.²¹ However, the use of hydrocortisone after a single dose of etomidate in patients who were not in septic shock does not influence the 28-day mortality.²² Because the number of the treated patients was comparable between the groups, one would expect the results to be influenced equally. Increased mortality following etomidate has been demonstrated in retrospective analyses of septic patients.¹⁴⁻¹⁶ Although the mentioned prospective studies, in patients with either various diagnoses or suspected sepsis, were not designed with mortality as a primary end point, the mortality outcomes are comparable to the present study.^{9,10} A shortcoming in large prospective studies studying sepsis is that on admission the diagnosis of sepsis is not always sure. For example, Tekwani et al. in their prospective study use the term 'suspected sepsis'.¹⁰ In conclusion, the present study does not demonstrate a difference in 28-day mortality, after a single dose of etomidate or a single dose of S-ketamine, administered to critically ill

Table 2. Results.

	Etomidate (n=161)	S-ketamine (n=140)	P
Mortality	61 (38%)	54 (39%)	0.998
LOS days mean (sd)	16 (25)	19 (27)	0.318
Norepinephrine hours mean (sd)	26 (31)	29 (29)	0.389
Cortisol three specimen n=64	n=64	n=73	
Cortisol concentrations µmol.l ⁻¹			
t=0 mean (sd)	0.89 (0.53)	1.04 (0.59)	0.122
t=24 hours	0.66 (0.37)*	0.69 (0.53)*	0.705
t=48 hours	0.67 (0.50)**	0.67 (0.50)*	1.000

LOS: length of stay in the intensive care department, following intubation; if a patient died within 28 days, after discharge from the intensive care department, the patient was not included in the LOS group. Norepinephrine infusion during 72 hours after intubation. Cortisol concentrations, if all three specimen, t=0, 24 and 48 hours, were present. *p<0.01, **p<0.02 compared to t=0.

patients with a diversity of primary diagnoses on the intensive care unit. Finally, the cortisol levels decrease after both the administration of etomidate and S-ketamine.

Trial registration: www.controlled-trials.com/ISRCTN39347168

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Nationale Kwaliteitsvisiting

Intensive Care

Aanvraag visitatie 2014



Voor medische afdelingen en zeker ook intensive care afdelingen is het essentieel dat kwalitatief goede zorg wordt verleend.

De kwaliteitsvisitingen worden verricht aan de hand van de richtlijn 'Organisatie en werkwijze op intensive care afdelingen voor volwassenen in Nederland' (2006) door NKIC getrainde intensivisten en IC-verpleegkundigen. De visitingen hebben tot doel behulpzaam te zijn bij het verbeteren van de kwaliteit van zorg op de intensive care.

Graag nodigen wij uw intensivecareafdeling uit om deel te nemen aan een kwaliteitsvisiting in 2014. Voor beschikbare data en aanvullende informatie kunt u contact opnemen met het NVIC secretariaat via e-mail: secretariaat@nvic.nl, of per telefoon: 030-6868761.