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Relative adrenal insufficiency in critically ill patient after rapid sequence intubation: KETASED ancillary study☆

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ABSTRACT

Purpose: Relative adrenal insufficiency (RAI) has been reported as a predictor of mortality in septic patient; however, its effects on mortality and outcomes for critically ill patients remain debatable. The objective of this study was to assess the effect of RAI on prognostic outcomes in patients after out-of-hospital rapid sequence intubation (RSI) and factors associated with the onset of RAI.

Patients and methods: A prespecified ancillary study of KETASED, a randomized prospective multicenter trial, was conducted. Three hundred ten patients who underwent RSI in an out-of-hospital setting had baseline cortisol and adrenocorticotropic hormone response test measurements within 24 hours of intensive care unit admission and were included.

Results: The mean (SD) age was 55 (19) years, with a mean (SD) Sequential Organ Failure Assessment score of 9 (4). Two hundred forty-seven (69%) patients presented with RAI. Baseline characteristics were similar between patients with and without RAI, except for the use of etomidate as a sedative agent (63% of patients with RAI vs 21%, $P < .001$), and history of chronic kidney disease. There was no difference in terms of 28-day mortality between the 2 groups (21% vs 19%, $P = .65$) and in terms of other 28-day prognosis end points.

Conclusion: In critically ill patients who require RSI, RAI is common and is not associated with worsened outcomes in our cohort.

1. Introduction

Early onset of relative adrenal insufficiency (RAI) in critically ill patients has been widely described [1-10]. Relative adrenal insufficiency implies an insufficient level of cortisol, being either a low level of basal cortisol or insufficient response to stimulation with adrenocorticotrophin hormone (ACTH). It indicates an inability of the hypopituitary-adrenal axis to adapt to increased needs in critical state [4]. Following the recent recommendations, *RAI* is defined by a random cortisol level of less than 10 μg/dL (<276 nmol/L) or a rise inferior to 9 μg/L (<250 nmol/L) after administration of 250 μg of ACTH [10].

Relative adrenal insufficiency has been reported as a predictor of mortality in septic patients [11-13]. Clinical equipoise remains on the effects of RAI on mortality and outcomes for general critically ill patients [14,15]. Furthermore, etomidate administration seems to be a major independent risk factor for RAI potentially associated with increased mortality [16,17]. However, KETASED study demonstrated measurable adrenal suppression but no evidence of adverse outcome related to a single bolus of etomidate for rapid sequence intubation (RSI) in patients with various types of shock. Different studies report controversial independent risk factors for RAI such as Sequential Organ Failure Assessment (SOFA) score, low platelet count, hypoalbuminemia, low pH, low bicarbonate [18], female sex [19], and low sodium and glucose [20]. Because none of the previous studies were controlled on the decision to use etomidate as a sedative agent, suspected risk factors must be assessed in an independent manner of the choice of sedative drug.

We undertook an ancillary study of the KETASED study, a trial that assessed early and 28-day morbidity after a single dose of etomidate or ketamine used for emergency intubation [21]. The objectives of the present study were to determine risk factors for early onset of RAI in a mixed population of critically ill patients and to assess the effect of RAI on mortality and other prognostic outcomes.

☆ Conflict of interest: None.

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2. Methods

2.1. Study setting and patients

This is an ancillary study from the KETAmine SEDation trial [15], a multicenter randomized study that compared early and 28-day morbidity after a single dose of etomidate or ketamine, registered in ClinicalTrials.gov under the number NCT00440102. Patients who underwent RSI were prospectively recruited from 12 emergency medical services or emergency departments and randomly assigned to received ketamine or etomidate as the sedative agent. The study was approved by local ethics committee (Comite de Protection des Personnes Ile-de-France Paris X, Aulnay-sous-bois, France; number AOM06103). Informed consent was waived at randomization because we recruited patients who needed urgent intubation, therefore with no capacity to consent. Informed consent was sought when the improved state of the patient allowed him/her to understand and sign. If not, according to the French law of Ethics, the consent from a relative or legal representative was sought.

From April 2007 to February 2008, for the KETASED study, we prospectively enrolled patients older than 18 years who needed emergency sedation for RSI. Patients in cardiac arrest, pregnant women, and patients with known contraindications to succinylcholine, ketamine, or etomidate were excluded. A 1:1 ratio randomly assigned patients to receive either etomidate (0.3 mg/kg) or ketamine (2 mg/kg), in combination with a paralytic agent (succinylcholine, 1 mg/kg). After the single dose of the sedative agent has been administrated and tube placement has been confirmed, sedation was maintained with the use of a standardized combination of midazolam and fentanyl or sufentanil. Intubation was performed in all cases by a senior emergency physician.

We included for this analysis all patients who had an evaluation of their adrenal function in the first 24 hours of intensive care unit (ICU) stay, namely, an analysis of random baseline cortisol level and its values 30 and 60 minutes after ACTH stimulation (250 μg of Synacten; Novartis, Stein, Switzerland). Conversely to the KETASED study, we included patients discharged from the ICU before 3 days (modified intention to treat in the KETASED study). Patients who died before reaching the hospital were excluded because no assessment of their adrenal function could have been processed. *Early onset of RAI* was defined by a random cortisol level of less than 10 μg/dL (<276 nmol/L) or a rise inferior to 9 μg/L (<250 nmol/L) after administration of 250 μg of ACTH [10] in the first 24 hours of ICU admission.

2.2. Data collection

We collected the patients' demographic and clinical characteristics at the time of recruitment, that is, before randomization, and data pertaining to their subsequent ICU stay. We used the SOFA score to assess the function of each of the 6 major organs, for an aggregate score ranging from 0 to 24 [22]. *Initial SOFA score* was defined as the sum of the worst values for each item collected during the first 24 hours. We recorded maximum SOFA score during the 28-day follow-up period [23] and calculated the delta-SOFA as the difference between maximum and initial SOFA score. The complete method details can be found in the original article [21].

2.3. Outcome

Primary end point for this substudy analysis was the occurrence of RAI. We sought to study the factors associated with the early onset of RAI. Secondary end points included 28-day mortality, mean and delta-SOFA score, vasopressor, and ventilator-free days at day 28.

2.4. Statistical analysis

Data are expressed as mean (SD) for normally distributed variables, median (interquartile range) for non-Gaussian quantitative variables, and as numbers and percentages for categorical variables. Normality of the distribution was checked using the Kolmogorov-Smirnov test. Quantitative data were compared using the Student *t* test or Wilcoxon rank sum test for normally or nonnormally distributed variables, respectively. Categorical data were compared using χ^2 test or Fisher exact test, as appropriate. Univariate analysis was used to assess the association between risk factors and the occurrence of early-onset RAI and between RAI and early and 28-day mortality and morbidity. To identify the independent factors associated with RAI, variables with *P* values less than .10 in univariate analysis were then considered for multivariate analysis and were analyzed in multiple 2 * 2 analyses to assess first-order interaction and confounding by fitting multiplicative models. Finally, variables identified from this selection were entered into a backward step-by-step logistic regression model. Goodness of fit of the model was then assessed by using the Hosmer-Lemeshow test. 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 comparisons were 2 tailed, and a *P* value less than .05 was required to reach statistical significance. Analyses were done with SAS statistical software 9.3 (SAS Institute Inc, Cary, NC).

3. Results

Of the 650 patients included in the KETASED study, 310 had an evaluation of their adrenal function in the first 24 hours and were analyzed. The mean (SD) age was 55 (19) years, and 165 (53%) were men. Initial SOFA score was 9 ± 4, and 155 (50%) were sedated with etomidate for RSI. Main reasons for emergency intubation were coma for 229 (74%) of them, acute respiratory failure for 46 (15%), and shock for 31 (10%). Relative adrenal insufficiency occurred in 214 (69%) of our 310 analyzed patients. Baseline characteristics are expressed in Table 1.

Characteristics on admission did not differ between the 2 groups (Table 1), except for the choice of etomidate as a sedative agent (63% of patients with RAI vs 21% without RAI, $P < .001$) and a history of chronic kidney disease (5% vs 0%, $P = .03$). Patient profile was similar with same degree of severity on admission appreciated by SOFA score and Simplified Acute Physiological Score II (Table 1).

In the multivariate analysis, factors associated with RAI were the use of etomidate as a sedative agent (odds ratio [OR], 6.28; 95% confident interval [CI], 3.54-11.15; $P < .0001$), diabetes mellitus (OR, 0.42; 95% CI, 0.18-0.96; $P = .04$), and diastolic blood pressure (OR, 1.02; 95% CI, 1.00-1.03; $P = .03$). The Hosmer and Lemeshow goodness-of-fit test indicated that the logistic model was a good fit.

All-cause 28-day mortality was of 20%, with similar rates for patients with or without early onset of RAI: 21% vs 19%, respectively, $P = .65$. We did not find any association between early onset of RAI and other markers of morbidity (Table 2).

Of note, the presence of RAI had no impact on the choice to start steroid regimen in the ICU: 14% of patients without RAI received hydrocortisone course vs 12% of patients with RAI ($P = .55$).

4. Discussion

Our study is the first to investigate the predictors and effect on mortality of early onset RAI in patients undergoing RSI. Our sample comprises one of the largest prospective databases of mixed ICU patients with initial evaluation of their adrenal function. From the initial database of the KETASED trial, with 655 randomized patients, we included 310 who had an initial assessment of their adrenal function. Our results suggest that early onset of RAI is not associated with increased mortality, or any other prognostic outcome.

It is now widely accepted that the use etomidate is associated with increased risk of RAI [17,16]. However, controversy remains whether it is associated with mortality in acutely ill patients, even within the