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Ketamine May Be Useful for Intubation in Critically Ill Patients CME

News Author: Laurie Barclay, MD
CME Author: Désirée Lie, MD, MSEd

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July 9, 2009 — Ketamine is a safe, valuable alternative to conventional etomidate for use as a sedative during intubation in critically ill patients, according to the results of a randomized controlled, single-blind trial reported online in the July 1 issue of *The Lancet*.

"Critically ill patients often require emergency intubation," write Patricia Jabre, MD, and colleagues from the KETASED Collaborative Study Group. "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."

At 12 emergency medical services or emergency departments and 65 intensive care units in France, 655 patients requiring sedation for emergency intubation were prospectively enrolled and randomly assigned by a computerized random-number generator list to receive 0.3 mg/kg of etomidate (n = 328) or 2 mg/kg of ketamine (n = 327) for intubation. Group assignment was known to only the emergency medicine physician enrolling patients.

The main outcome measure was the maximal score of the sequential organ failure assessment (SOFA) during the first 3 days in the intensive care unit. Analysis was by modified intent-to-treat, with exclusion from analysis of patients who died before reaching the hospital and those discharged from the intensive care unit earlier than 3 days.

Data were analyzed for 234 patients in the etomidate group and 235 in the ketamine group. Both groups had statistically similar mean maximal SOFA scores (10.3 ± 3.7 for etomidate vs 9.6 ± 3.9 for ketamine; mean difference, 0.7; 95% confidence interval [CI], 0.0 - 1.4; *P* = .056). Both groups had a median intubation difficulty score of 1 (interquartile ratio, 0 - 3; *P* = .70) suggesting similar intubation conditions.

Compared with the ketamine group, the etomidate group had a significantly higher percentage of patients with adrenal insufficiency (odds ratio, 6.7; 95% CI, 3.5 - 12.7). No serious adverse events occurred with either study drug.

"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," the study authors write.

Limitations of this study include possibly insufficient power to show a significant increase in morbidity rates associated with etomidate use in patients with sepsis.

In an accompanying comment, Dr. Volker Wenzel and Dr. Karl H. Lindner, from Innsbruck Medical University in Innsbruck, Austria, note that successful emergency intubation of critically ill patients depends on pharmacologic knowledge as well as manual skills and clinical experience. Unfortunately, tightening regulations of the European Union hinder trials of commercially noninteresting pathology such as multiple trauma.

"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," Drs. Wenzel and Lindner write. "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."

The French Ministry of Health supported this study. The study authors and editorialists have disclosed no relevant financial relationships.

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Clinical Context

Rapid sequence intubation with administration of a paralytic and a sedative agent is common. Etomidate is a sedative-hypnotic most often used but can cause reversible adrenal insufficiency and increase morbidity rates in critically ill patients who require intubation.

This is a prospective, single-blind, randomized controlled trial conducted at 12 emergency medical services or emergency departments and 65 intensive care units in France to compare the morbidity and mortality rates associated with etomidate and ketamine administered with rapid sequence intubation in critically ill patients.

Study Highlights

- The emergency medical services were ambulance stations equipped with mobile intensive care units with a driver, nurse, and senior emergency medicine physician as a minimum team.
- Patients were included if they were 18 years or older, were critically ill, and needed sedation for emergency rapid sequence intubation.
- Excluded were patients with cardiac arrest and known pregnancy, those who died before hospitalization, or those who were discharged within 3 days of intensive care unit admission.
- Patients were randomly assigned to etomidate 0.3-mg/kg intravenous bolus or ketamine as 2-mg/kg intravenous bolus.
- The emergency physician was aware of assignment, but other staff members were masked.
- Succinylcholine was given immediately after the sedative as a 1-mg/kg intravenous bolus, and continuous sedation was initiated with a standardized protocol of midazolam combined with fentanyl or sufentanil.
- The SOFA, with a scale of 0 to 4 (aggregate scores, 0 to 24), was used to assess organ dysfunction, with a higher score indicating greater dysfunction.
- Adrenal insufficiency was defined as a random cortisol concentration of less than 276 nmol/L or a difference from baseline of less than 250 nmol/L at 30 or 60 minutes after an adrenocorticotropin hormone (ACTH) stimulation test.
- A patient was defined as a nonresponder if the increase in cortisol did not exceed 250 nmol/L at these times.
- The intubation score was computed with a value greater than 5 synonymous with difficult intubation.
- Primary endpoint was the maximum SOFA score during the first 3 days in the intensive care unit.
- Secondary endpoints were change in SOFA score from baseline in the 28-day follow-up, mortality, duration of stay in the intensive care unit, use of catecholamines, and safety assessed by adverse events and ACTH response.
- 650 patients were analyzed for the study, and intent-to-treat analysis was conducted in 469 patients (234 in the etomidate group and 235 in the ketamine group).
- Coma was the main reason for intubation.
- Trauma was the final diagnosis in 22% and sepsis in 16%, with less frequent diagnoses being stroke, drug poisoning, cardiogenic shock, and respiratory failure.
- Mean age of the patients was 58 years, more than 50% were men, and one third had hypertension.
- The maximum SOFA score did not differ significantly between the 2 groups.
- The change in SOFA score from baseline also did not differ significantly.
- There were no differences in other outcomes of 28-day mortality, catecholamine-free days at day 28, percentage needing catecholamine support, duration of weaning, and length of stay in the intensive care unit.
- Basal cortisol level was lower in the etomidate group.
- The percentage of patients with adrenal insufficiency was significantly higher in the etomidate group (odds ratio, 6.7).
- More than 80% of patients receiving etomidate had adrenal insufficiency and were nonresponders to the ACTH test.
- Mortality rate did not differ in responders and nonresponders to the ACTH test.
- Rates of serious adverse events were similar for the etomidate group and the ketamine group.

- The authors concluded that a bolus dose of etomidate was not associated with increased morbidity or mortality rate vs ketamine in critically ill patients requiring rapid sequence intubation.
- They also noted that etomidate affected the adrenocortical axis significantly more than ketamine and that ketamine was a safe and valuable alternative to etomidate.

Clinical Implications

- Use of etomidate and ketamine in rapid sequence intubation of critically ill patients is associated with similar morbidity and mortality rates.
- Use of etomidate vs ketamine is associated with higher rates of adrenal insufficiency and similar rates of adverse events.

CME Test

According to the study by Jabre and colleagues, ketamine was superior to etomidate in critically ill patients requiring rapid sequence intubation for which of the following outcomes?

- Maximum SOFA score
- Length of stay in the intensive care unit
- Catecholamine-free days
- None of the above

Which of the following outcomes is *most* likely to occur at a higher rate in critically ill patients given etomidate vs ketamine when receiving rapid sequence intubation?

- Mortality
- Serious adverse events
- Adrenal insufficiency
- All of the above

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Author(s)

Laurie Barclay, MD

Laurie Barclay, MD, is a freelance writer and reviewer for Medscape.

Disclosure: Laurie Barclay, MD, has disclosed no relevant financial relationships.

Editor(s)

Brande Nicole Martin

Brande Nicole Martin is the News CME editor for Medscape Medical News.

Disclosure: Brande Nicole Martin has disclosed no relevant financial information.

CME Author(s)

Désirée Lie, MD, MSEd

Clinical Professor, Family Medicine, University of California, Orange; Director, Division of Faculty Development, UCI Medical Center, Orange, California

Disclosure: Désirée Lie, MD, MSEd, has disclosed no relevant financial relationships.

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Target Audience

This article is intended for primary care clinicians, emergency medicine specialists, intensivists, anesthesiologists, and other specialists who care for patients who require emergency intubation.

Goal

The goal of this activity is to provide medical news to primary care clinicians and other healthcare professionals in order to enhance patient care.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Compare the morbidity rates associated with etomidate vs ketamine used for rapid sequence intubation in critically ill patients.
- Describe adrenal insufficiency and adverse affects associated with the use of etomidate vs ketamine for rapid sequence intubation.

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