

COMMENTARY

Etomidate for intubation of patients who have sepsis or septic shock – where do we go from here?

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See related research by Jung *et al.*, <http://ccforum.com/content/16/6/R224>

Abstract

Etomidate is an intravenous induction agent that is associated with hemodynamic stability during intubation. The agent is therefore attractive for use in critically ill patients who have a high risk of hemodynamic instability during this procedure. However, etomidate causes adrenal suppression, which itself has been associated with increased mortality in critically ill patients. The ongoing debate surrounding use of etomidate is thus centered on the immediate favorable hemodynamic profile versus the long-term risks of adrenal insufficiency, particularly in patients who have severe sepsis or septic shock.

In this issue of *Critical Care*, Jung and colleagues reported on their single-center observational cohort study that compared etomidate with other induction agents to facilitate intubation in the 48 hours before the onset of shock in patients who had septic shock [1]. Based on local practice, all of these patients received hydrocortisone supplementation after a corticotropin stimulation test. This practice provided a unique opportunity to examine an important gap in the current literature: the risks and benefits of etomidate in septic shock in the context of universal hydrocortisone supplementation. Importantly, this study confirmed that immediate life-threatening complications, including severe hypotension, are common (37 of 102 patients) during the intubation period. Patients who received etomidate were

more severely ill at baseline, which may explain why their physicians chose to use this agent. Consistent with other published results [2–4], patients who received etomidate had lower serum cortisol concentrations after intubation and a higher percentage of nonresponse to the corticotropin stimulation test compared with patients who received another induction agent (79% vs. 52%, $P = 0.01$). Patients who received etomidate also required a longer duration of hydrocortisone supplementation and a higher cumulative dose of norepinephrine compared with the non-etomidate group. Multivariable Cox regression demonstrated a decreased mortality rate in patients who had received etomidate (hazard ratio = 0.33, 95% confidence interval = 0.12 to 0.90, $P = 0.03$) after adjusting for severity of illness. It is important to note that the mortality signal favoring etomidate was contrary to the authors' *a priori* hypothesis.

The current study adds considerably to the limited evidence concerning use of etomidate in patients who have severe sepsis or septic shock. A *post-hoc* analysis of the Corticosteroid Therapy of Septic Shock (CORTICUS) trial showed that patients who received etomidate were more likely not to respond to corticotropin and had an increased mortality rate at 28 days (43% vs. 31%, $P = 0.03$) compared with patients who did not receive etomidate [2]. Use of hydrocortisone did not appear to substantively modify this relationship [5]. In CORTICUS, the median time between receiving etomidate and randomization to steroids (or not) was 14.5 hours (interquartile range = 4.25 to 28.4 hours) [5]. In contrast, the patients in the current study received hydrocortisone within 9 hours (interquartile range 5 to 19 hours) of intubation. Time may therefore be an important effect modifier in this analysis. Indeed, other authors have suggested that a brief course of corticosteroids should be given to patients who have received etomidate [6].

Even if we take the results of this current study as evidence of equipoise in this issue, we have to ask ourselves 'What are the benefits of etomidate?' Use of this drug is

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certainly associated with hemodynamic stability [7], which is why it is lauded as an agent for emergent rapid sequence induction [8]. However, there are several other means to achieve this goal. One possibility is to improve the process of care during intubation. Jaber and colleagues (same research group who authored the paper under discussion) have previously demonstrated a dramatic reduction in life-threatening cardiopulmonary complications from 34% to 21% ($P = 0.03$) after the introduction of a bundle of recommendations aimed at preventing intubation complications [9]. Of note, standardized induction agents, including etomidate, are an important component of this bundle, which also includes a fluid bolus, two operators, and the early use of vasopressors. Another possibility is to use alternate induction agents that have similar hemodynamic profiles to etomidate. In the KETASED trial, patients who required emergency intubation were randomized to etomidate or ketamine for induction [10]. There was no difference in terms of intubating conditions or immediate life-threatening complications between the two groups. Importantly there was also no difference in mortality between the two groups, although only 16% of the patients had sepsis. However, use of etomidate was associated with a much higher risk of adrenal insufficiency (86% vs. 48%, $P < 0.0001$) when compared with ketamine.

The central question regarding use of etomidate in patients who have severe sepsis and septic shock still remains 'Where do we go from here?' This study by Jung and colleagues adds to the debate and asks further important questions. In particular, 'Does early steroid supplementation modify the risk of etomidate in these patients?' However, in light of the conflicting data on clinical outcomes after use of etomidate and a readily available alternative agent that has a similar hemodynamic profile without the risk of adrenal suppression, namely ketamine, the use of etomidate in patients who have severe sepsis or septic shock continues to be controversial and potentially problematic.

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Competing Interests

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