Controversies

Should etomidate be used for rapid-sequence intubation induction in critically ill septic patients?

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Abstract  Etomidate is an agent often used by emergency medicine physicians for rapid-sequence intubation induction of critically ill patients because of its reliable pharmacokinetics and cardiovascular stability. Etomidate is known to inhibit endogenous cortisol production through inhibition of 11β-hydroxylase. Previous studies in undifferentiated emergency department patients and healthy, elective surgical patients have shown this effect to be only transient and not clinically significant. Recent retrospective studies in the pediatric and adult intensive care literature have shown an association between a single induction dose of etomidate in critically ill septic patients and sustained suppression of the adrenal axis with an increase in mortality. It is unknown at this time if any increase in mortality associated with etomidate-induced adrenal suppression would be offset by concomitant corticosteroid administration. Aggressive resuscitation of septic patients with fluids, antibiotics, and vasopressors has been shown to significantly reduce mortality and may allow for the use of alternative agents that had previously been discouraged because of concern for hemodynamic collapse during intubation. A prospective randomized trial in septic patients of etomidate induction with early corticotropin stimulation testing or corticosteroid supplementation vs the use of alternative induction agents with enough power to detect differences in mortality is needed to further address this clinical dilemma.

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1. Introduction

Etomidate is considered by many to be the drug of choice for rapid-sequence intubation (RSI) induction of patients in the emergency department (ED) who have or are at risk for hemodynamic collapse [1]. It has a rapid onset of action (<60 seconds), reliable pharmacokinetics, and cardiovascular stability while dealing with patients who are critically ill. Furthermore, etomidate has no effect on intracranial pressure.

Etomidate is known to inhibit adrenal steroidogenesis, and thus cortisol production, through its inhibition of 11β-hydroxylase [2], thus limiting the endogenous stress response that is paramount in septic patients. These patients are continuously subjected to high stress, have limited corticosteroid reserve, and require adequate cortisol levels to maintain homeostasis [3]. Etomidate has also been shown to affect levels of interleukin 6 [4] and 10 [5], may impact circulating lymphocyte levels [4], and may interfere with proinflammatory mediators that could be protective in sepsis.

Previous studies have demonstrated only transient (<4-12 hours) adrenal suppression after administration of
etomidate and, more importantly, no clinically significant reduction in blood pressures or clinical outcomes. However, these studies were small and looked at undifferentiated ED populations [6] or healthy adults undergoing elective surgical procedures [7,8]. Several recent retrospective studies in the pediatric and adult intensive care literature have shown an association between critically ill patients who had received etomidate during intubation and sustained adrenal insufficiency with increased mortality. In fact, the intensive care unit (ICU) literature [9] calls for a ban of its use from that setting, and the anesthesia literature [10] urges reconsideration of its use in emergency and high-risk cases.

In 2002, Annane [11] reported a reduction in the risk of mortality after low-dose corticosteroid administration in critically ill patients with septic shock in the ICU setting who failed corticotropin stimulation testing (CST). Almost 2 years into this study, the investigators had to amend the eligibility criteria to exclude patients who had received etomidate for induction. Sixty eight of the 72 patients (94.4%) who had received a single induction dose of etomidate to that point failed their CST, compared with 71% of those who had not received etomidate [12]. A subgroup analysis of the 68 CST nonresponders who had received etomidate revealed significantly higher ICU and hospital mortality rates in those who had been randomized to receive placebo vs corticosteroids [13] (75.7% vs 54.8%, respectively; \( P = .0315 \)).

Malerba et al [14] retrospectively looked at a cohort of 62 patients who were mechanically ventilated for more than 24 hours in an ICU setting. Of these patients, 33.9% had severe sepsis, 24.2% had cardiogenic shock, 17.7% had severe neurologic illness, 9.7% were postoperative, and 6.5% were poisonings. A CST differentiated these patients into 27 nonresponders and 35 responders. Multivariate analysis demonstrated that etomidate administration was related to adrenal insufficiency, with an odds ratio of 12.21 (95% confidence interval [CI], 2.99-49.74) for being a nonresponder. The nonresponders demonstrated more organ dysfunction, greater need for vasopressors, and higher mortality rates with 70.4% of nonresponders vs 31.4% of responders dying in the ICU (\( P < .005 \)).

Recently, Mohammad et al [15] echoed the findings of the above studies with their findings of adrenal insufficiency in patients with septic shock who had received etomidate. They retrospectively reviewed the records of 152 patients with septic shock who had undergone CST. Of these patients, 38 had received etomidate before CST, with a mean interval of 7 hours between administration of etomidate and testing. The incidence of relative adrenal insufficiency was 76% in patients who had received etomidate (95% CI, 67%-87%) and 51% (95% CI, 42%-60%) in those who had not received etomidate (\( P = .0077 \)).

There are fewer studies on the incidence of adrenal insufficiency and its effect on mortality in children with sepsis. Although not directly addressing our specific clinical question, because of their exclusion of children who had received etomidate, Pizarro et al [16] looked at the incidence of absolute and relative adrenal insufficiency in children with septic shock. All of the children with absolute adrenal insufficiency and 80% of the children with relative adrenal insufficiency had catecholamine-resistant shock (defined as shock that persisted despite the use of fluid resuscitation and the use of epinephrine or norepinephrine) compared with 44% of the children with adequate adrenal response. There was an insignificant trend toward increased mortality in children who had absolute (50%) or relative (53%) adrenal insufficiency compared with patients with adequate CST (28%) response. Brinker et al [17] studied 60 children with meningococcal sepsis and found that nonsurvivors had lower bioavailable cortisol levels and higher adrenocorticotropic hormone (ACTH) levels than survivors. On multiple regression analysis, the use of etomidate was associated with a decrease in mean cortisol-ACTH ratios by 84%. Interestingly, this study found no difference in cortisol-ACTH ratios between children who were intubated without etomidate and those who were not intubated at all, with all children who were intubated (with or without etomidate) having higher disease severity scores. This suggests that, for this cohort, intubation with etomidate had a stronger correlation with low cortisol-ACTH ratios than disease severity. Although this study did not specifically look at differences in mortality from etomidate administration, 7 of the 8 deaths were in children who had received etomidate.

2. Discussion

Previous emergency medicine literature has noted etomidate as the induction agent of choice for RSI in the ED [1,18]. However, the evidence available at that time concluded that etomidate’s inhibition of the adrenal axis was only transient (<4-12 hours) and not clinically significant. The recent studies reviewed above show an association between critically ill septic patients who had received etomidate and sustained (>24 hours) adrenal suppression with increased mortality. These recent studies are all flawed in that they are retrospective cohorts and thus cannot control for confounding variables. It is possible that the increased rates of adrenal insufficiency found in patients who had been intubated with etomidate serves only as a marker of those patients with increased disease severity (with such patients being intubated with etomidate because of their dire clinical picture and the physician’s concern for hemodynamic collapse during intubation). Nevertheless, the recurrent finding of increased adrenal insufficiency in critically ill septic patients who had received etomidate for intubation cannot be ignored.

Some studies have shown a benefit to corticosteroid administration in critically ill patients with adrenal...
insufficiency [3,11], and some authors have argued that the possible mortality cost of adrenal suppression by etomidate induction may be completely offset by concomitant corticosteroid administration [19]. A study presented at the Critical Care Society meeting in February 2007 and available only in abstract form may lend credence to those who would recommend septic patients be intubated with etomidate and be given concomitant corticosteroids. Dmello et al [22] noted in their retrospective review in an ICU setting that septic patients who had received etomidate for induction had nonsignificant differences in mortality (risk ratio, 0.88; 95% CI, 0.64-1.21; P = .43) but significantly increased corticosteroid requirements (risk ratio, 1.92; 95% CI, 1.27-2.92; P = .001). However, the use of corticosteroid replacement in septic patients with adrenal insufficiency is still hotly debated and not universally accepted [12,13,20,21]. The soon-to-be-completed Corticosteroid Therapy of Septic Shock (CORTICUS) study may offer further guidance on the potential benefit of corticosteroid replacement in septic patients with adrenal insufficiency.

The use of alternative RSI induction agents in septic patients, whose role has been reduced because of the widespread acceptance of etomidate as the agent of choice for RSI, may need to be reconsidered. Ketamine offers many of the advantages of etomidate such as rapid onset of action, reliable pharmacokinetics, and stable hemodynamics [1]. However, its use in the ED for RSI induction has been limited by its theoretical increase in intracranial pressure. Although certainly an issue in trauma patients, this rise in intracranial pressure may be less of a concern in the appropriately selected septic patient. Midazolam is also commonly used for RSI induction, but its role has been reduced because of multiple studies that have shown an increased rate of hypotension from its use [20-23]. However, in all of these studies, the decrease in blood pressure during induction was transient (<15 minutes), and there was no resultant increase in the need for vasopressors. Recent studies have not shown any difference in rates of hypotension when comparing midazolam with etomidate [24,25], and we are not aware of any studies that have ever shown an increased rate of mortality from midazolam-associated hemodynamic collapse.

The diverse clinical presentations of critically ill septic patients challenges even the most experienced emergency medicine physicians. The art of treating each unique presentation optimally impedes the development of strict stepwise algorithms. Some of these patients will arrive to the ED in obvious hemodynamic collapse and in need of immediate intubation before early goal-directed therapy [26] can be instituted. In these patients, etomidate may offer the best risk-reward profile for maintenance of the patient’s tenuous hemodynamic status. Coordinated protocols with EDs and ICUs should be considered for early CST or immediate low-dose replacement of corticosteroids in patients who receive etomidate for induction (depending on how your ICU treats patients with adrenal insufficiency). For those septic patients who arrive relatively stable without the need for immediate intubation, optimal treatment of the patient may involve aggressive early goal-directed therapy [26] with central line placement, fluid resuscitation, antibiotic administration, and vasopressor use. Intubation of these patients with their clinical status more stabilized may allow for alternative induction agent use.

The question of whether etomidate truly causes increased adrenal suppression and mortality in septic patients or merely acts as a marker for disease severity will not be truly answered until a prospective randomized study is performed. However, with the above-mentioned studies in mind, a prospective, blinded study with the etomidate group not receiving corticosteroid replacement may be very difficult to perform and could possibly raise ethical concerns for institutional review boards.

3. Conclusion

In summary, there is mounting evidence that the adrenal suppression after RSI induction with etomidate may not be as transient and benign as the emergency medicine literature has previously suggested. Emergency medicine physicians should be aware of the potential risk for sustained adrenal suppression and increased mortality with etomidate use in critically ill septic patients. Aggressive resuscitation of septic patients with fluids, antibiotics, and vasopressors has been shown to significantly reduce mortality and may allow for the use of alternative agents that had previously been discouraged because of concern for hemodynamic collapse during intubation. Protocols should be considered between EDs and ICUs for early CST or corticosteroid supplementation in patients who do receive etomidate. A prospective randomized trial of etomidate induction with early CST or corticosteroid supplementation vs the use of alternative induction agents with enough power to detect differences in mortality is needed to further address this clinical dilemma.

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