Clinical Controversies: Etomidate as an Induction Agent for Endotracheal Intubation in Patients With Sepsis

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor’s Note that summarizes important concepts. Participation as an authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

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Editor’s note: Because it exhibits many favorable characteristics, including rapid onset, minimal respiratory depression, and preservation of hemodynamic stability, etomidate has frequently been used as an induction agent for endotracheal intubation of septic patients. This practice has recently been questioned in light of studies demonstrating that even a single dose of etomidate may interfere with cortisol production and produce relative adrenal insufficiency in critically ill patients. In this installment of Clinical Controversies, pro and con advocates present opposing perspectives and discuss the available evidence and arguments that must be considered in deciding to embrace or abandon the use of etomidate as an induction agent for endotracheal intubation of septic patients.

CONTINUE TO USE ETOMIDATE FOR INTUBATION OF PATIENTS WITH SEPTIC SHOCK

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Etomidate, long considered safe and reliable for emergency intubation, has recently come under fire. Despite the lack of a single prospective, randomized study scientifically demonstrating any adverse patient outcome related to etomidate’s transient inhibition of 11β-hydroxylase, the enzyme involved in the final step of cortisol production, some authors have called for a ban of the use of etomidate in sepsis. No cortisol level was below the normal range, but significantly more patients in the etomidate group had reduced response to cosyntropin. Mohammad et al. retrospectively analyzed 152 patients with septic shock who had a cosyntropin stimulation test. There were no differences in serum cortisol levels between the patients who had received etomidate 7 to 10 hours before study enrollment and nonetomidate patients, but 76% of etomidate versus 51% of nonetomidate patients had “relative adrenal insufficiency,” as defined by the authors. From these and other studies, it is reasonable to conclude that a single dose of etomidate increases the likelihood that a patient with sepsis will have a reduced response to exogenous cosyntropin. Cortisol levels may similarly be reduced, but not below the normal range.

Although no prospective, randomized study has shown an increase in mortality related to a single use of etomidate in patients with sepsis, several authors have improperly claimed that etomidate increases mortality. Lipiner-Friedman et al. retrospectively analyzed data from the Corticus sepsis study and reported that for patients who received etomidate, nonsurvivors had both lower cortisol levels and less response to exogenous cosyntropin than survivors. The authors paid scant attention to
the fact that the actual cortisol differences between nonsurvivors and survivors in the etomidate group were small, that all cortisol levels were in the normal range, and that the reduction in cosyntropin response in the etomidate patient groups was less than that observed for nonetomidate patients. Although their own 95% confidence interval argues to the contrary, the authors inexplicably assert that etomidate is associated with an increased risk of death.

Studies conducted specifically to compare mortality in etomidate versus nonetomidate patients have failed to demonstrate any difference. Mohammad et al\(^3\) found no difference in mortality rates for shock patients receiving etomidate versus those who did not. Ray and McKeown\(^6\) found no increases in vasopressor use or mortality for septic shock patients receiving etomidate. Riché et al\(^7\) found no link between cosyntropin response and mortality and no difference in mortality between etomidate and nonetomidate patients with intra-abdominal sepsis. Sprung et al\(^8\) and the Corticus study group confirmed an association between etomidate and the likelihood of reduced adrenal response to cosyntropin. They appropriately avoided drawing any unsupported conclusions about the higher observed mortality in their (nonrandomized) etomidate patients.

Hypotension occurring at any time is associated with increased mortality in critically ill patients.\(^9\) Etomidate’s hemodynamic profile is superior to that of virtually all available induction agents. In patients with limited cardiovascular reserve, intubation and mechanical ventilation are often associated with hypotension, regardless of the induction agent used. Compounding this effect by using an agent that is known to decrease mean arterial blood pressure seems unnecessarily risky. Ketamine, which some consider a reasonable alternative to etomidate, is not available in many emergency departments or critical care units, is not well studied for this use, and is itself associated with adverse effects.

According to the supporting evidence, including that cited above, calls for a ban on etomidate for intubation in sepsis are not justified. Finfer\(^10\) states, “Perhaps the greatest service we can do our patients is to conduct the large, high-quality trials needed to base our clinical practice on truly robust evidence.” Etomidate opponents should advocate such a properly designed, randomized trial, lest they cause further harm by forcing those of us charged with resuscitation of these vulnerable patients to use agents much more likely to disturb their fragile hemodynamic balance, with potentially fatal consequences.

**Funding and support:** By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.
that a single dose of etomidate adversely affects adrenal gland function. Etomidate eliminates the adrenal’s response to adrenocorticotropic hormone through inhibition of 11β-hydroxylase, the same enzyme implicated in sepsis-associated adrenal dysfunction. It is this response to adrenocorticotropic hormone and not the serum cortisol level itself that correlates most with outcomes in sepsis.\textsuperscript{3,5,6} In the Schenarts et al\textsuperscript{7} study of etomidate use, 70% of patients experienced an abnormal cortisol response after a single etomidate dose, whereas in the Mohammad et al\textsuperscript{2} study, adrenal insufficiency was found in 76% of those receiving 1 dose of etomidate. den Brinker et al\textsuperscript{8} presented the most convincing evidence of etomidate’s depressive effects in their study of 60 children with meningococcal sepsis. Their analysis demonstrated that compared with etomidate-naive children, those receiving a single dose of etomidate demonstrated a 3.2-fold lower cortisol/11-deoxycortisol ratio, with a 4.1-fold higher adrenocorticotropic hormone/arterial lactate level. These findings indicate greater impairment of adrenal synthesis in the face of increased cortisol demand in etomidate-treated patients.

Emergency physicians have readily adopted etomidate as the agent of choice for rapid sequence intubation because it functions exceptionally well in the context of the ED.\textsuperscript{6,7} It has a relatively flat cardiovascular response curve and produces no immediate clinical findings. However, most ED stays are too brief to witness etomidate’s downstream adrenal actions, leading emergency physicians to believe that the drug’s endocrine actions are clinically insignificant.\textsuperscript{6,7}

To date there are no good prospective data condemning etomidate’s use in septic patients, although there are certainly retrospective data that are concerning. In the Lipiner-Friedman et al\textsuperscript{1} study of adrenal function in 477 patients with septic shock, a univariate analysis of predictors of hospital mortality demonstrated an odds ratio for death of 1.53 (95% confidence interval 1.06 to 2.26) for patients receiving etomidate. In the den Brinker et al\textsuperscript{8} meningococcal study, deaths occurred in 1 of 8 (12.5%) septic children intubated without etomidate compared with 7 of 23 (30%) of those intubated with etomidate ($P<.05$).

One proposed solution to etomidate’s adrenal-suppressive effect is the concurrent administration of hydrocortisone to patients receiving it for rapid sequence intubation.\textsuperscript{6} This approach is a reversal of the “clinically insignificant” argument for etomidate’s use and further interferes with the already compromised adrenal neurohormonal axis. The one study examining this issue is the Ray and McKeown\textsuperscript{9} retrospective review of pressor and steroid use in 159 septic shock patients. Their review demonstrated no improvement in mortality in septic patients receiving etomidate plus hydrocortisone compared with those receiving etomidate alone.

Etomidate’s use could be justified if no acceptable alternatives existed. However, emergency physicians have multiple options for sedation during intubation, and limiting rapid sequence intubation choices to a single agent should be no more acceptable than restricting physicians to a single antiarrhythmic or antibiotic. In normotensive patients, drugs such as propofol, methohexital, thiopental, and even midazolam are realistic sedative/intubation agents. In the more common hypotensive septic patient, ketamine may be the most appropriate rapid sequence intubation agent. In addition to providing hemodynamic stability during the intubation procedure, there is a growing body of experimental evidence suggesting that ketamine exerts a protective anti-inflammatory effect against the sepsis process itself.\textsuperscript{10}

Future evidence-based studies may ultimately prove that etomidate is a safe agent in septic patients requiring endotracheal intubation. However, given the information currently available, it is difficult to justify the use of this agent in any critically ill patients whose long-term survival is directly linked to the performance of their adrenal glands.

**Funding and support:** By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The author has stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement. Reprints not available from the author.

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doi:10.1016/j.annemergmed.2008.01.001

**REFERENCES**


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DIAGNOSIS:

Gonococcal conjunctivitis. Gonococcal conjunctivitis is a rare but devastating infection of the eye. There are 2 distinct forms, one affecting neonates and the other affecting sexually active adults. Transmission is by contact with infected urine or genital secretions, with the incubation period ranging from 3 to 19 days. There is a documented increase in infections during spring and summer.1 The infection is characterized by a hyperpurulent discharge that some have described as a "fountain of pus." Culturing ocular discharge makes the definitive diagnosis, but treatment must be instituted before culture results, given the aggressive nature of the infection. Gonococcal conjunctivitis can result in corneal perforation and vision loss in 24 hours. Treatment involves parenteral antibiotics, in addition to ocular irrigation and topical antibiotics. Given the emergence of Neisseria gonorrhoeae strains that are resistant to the quinolones, this patient was treated with intravenous ceftriaxone. If patients are treated before corneal destruction, outcomes are good, with preserved visual acuity.

REFERENCES
