The use of etomidate for rapid sequence induction in septic patients

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Abstract: There is continued debate about the clinical ramifications of single-dose etomidate for rapid sequence induction (RSI) in patients with sepsis. This history of this debate includes early studies identifying an association between etomidate infusions and mortality with adrenal suppression as a hypothesized mechanism. More recent data describing the high prevalence of adrenal insufficiency in patients with sepsis has prompted additional investigation as to the clinical effects of single-dose etomidate when utilized as an agent in RSI. Acknowledging the small number and heterogeneity of studies on this topic, we feel that the recent meta-analysis by Gu et al. provides an accurate and complete assessment of the existing literature on this topic. We continue to utilize etomidate for the purposes of RSI in this critically ill patient population and feel that the current data supports this position.

Keywords: Sepsis; intubation; etomidate

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Rapid sequence induction (RSI) is a common practice used to facilitate endotracheal intubation in critically ill patients. Single-dose etomidate provides rapid and effective sedation with minimal acute hemodynamic effect (1). While this pharmacological profile makes it an attractive option for RSI, etomidate has been shown to cause adrenal suppression. When utilized as an infusion, this effect can be profound enough to affect mortality (2). While it is also generally accepted that single dose etomidate likewise causes suppression of the adrenal axis, the clinical significance of this interaction remains poorly understood.

Etomidate was historically utilized as a constant infusion for sedation for mechanically ventilated patients, however data published in the early 1980s raised concern about its association with mortality (2). Numerous studies identified the effect of etomidate on cortisol synthesis through inhibition of 11-beta hydroxylase (3). Studies in humans examined etomidate use in patients undergoing elective surgeries, confirming in vivo suppression of the adrenal axis (4). Further research in the late 1990s and early 2000s examined this phenomenon in critically ill patients and found consistent effects on cortisol production, but were insufficiently powered to detect differences in mortality (5,6).

In 2006, Annane and colleagues reported that a majority of patients with severe sepsis and septic shock demonstrated some degree of adrenal insufficiency (7). Given the widespread usage of etomidate for RSI in critically ill patients (and therefore a large number of septic patients), studies have examined the effect of a single dose of etomidate on clinical outcome (mortality). However, the bulk of these investigations featured low enrollment and their results have been mixed; therefore the clinical significance of etomidate's induction of adrenal insufficiency in patients with septic shock remains unclear (8). In an effort to pool the available data, several groups have published meta-analyses and systematic reviews on this topic.

In “Single-Dose Etomidate Does Not Increase Mortality in Patients with Sepsis”, published in CHEST earlier this year, Gu et al. argue that while a one-time administration of etomidate likely induces adrenal insufficiency, this effect is not associated with increased mortality (9). The authors identified eighteen articles (two randomized control trials and sixteen observational studies) including a total of 5,552 patients. After pooled analysis, single-dose etomidate was not associated with mortality in patients with sepsis in either the randomized control trials (RR 1.2, 0.84-1.72, P=0.23) or the
observational studies (RR 1.05, 0.97-1.13, P=0.748).

These findings come in contrast with those of two other recently published meta-analyses (10,11). Albert and colleagues found an association between etomidate and mortality (RR of 1.22, 95% CI: 1.11-1.35) in a subset analysis of seven studies examining the effect of etomidate on mortality in patients with sepsis. The authors utilized a fixed-effects model despite the high heterogeneity between the studies (I²=75%). Gu and colleagues correctly point out that a random-effects model is appropriate for this analysis; had this been utilized, no association with mortality would have been found. Chan and colleagues published a meta-analysis in 2012 which demonstrated an association between etomidate and mortality. With several more recent studies performed on this subject, Gu and colleagues’ analysis has the advantage of including an additional 3,263 patients. Given the large number of included patients and robust statistical analysis, this seems to be the definitive summary of data available at the present time.

The on-going debate on this topic is illustrative of a common theme in clinical research; correlating identified physiological interactions with meaningful outcomes. In this case, we are tasked with establishing a link between etomidate’s effect on the adrenal axis (a fact that seems well-proven in the current body of literature) with mortality. The sheer number of potential confounding factors that might influence a patient’s outcome may outweigh the effect of a single dose of etomidate early in the patient’s course. A more proximal outcome (such as duration of vasopressor therapy after onset of shock) might be more plausibly associated with RSI medications and could be considered in future studies.

One factor that is poorly accounted for in the majority of the present studies is the drug regimen utilized in the control groups. Only three of the studies described a comparison regimen to etomidate (12-14). The effects of various induction agents on hemodynamic profile during RSI are complex; however, literature would suggest that the choice of induction agent has very real acute physiological effects (15). When arguing that etomidate does not increase mortality compared to other regimens, one must consider what drugs were used in the control groups. Might the deleterious hemodynamic effects of other induction regimens (high dose propofol for example) play a role in patient outcome?

Gu and colleagues offer a robust and complete synthesis of the presently available data on this topic, and we appreciate their contribution to the body of literature. Any meta-analysis on this topic is limited by the small number of randomized control trials and overall heterogeneity of the data. Further studies are certainly needed to definitively lay this question to rest. We agree with the authors’ conclusions that etomidate is associated with a real suppression of the adrenal axis, but that this relationship has not been shown to translate into meaningful deleterious clinical outcomes. We continue to utilize etomidate for RSI in patients with sepsis for what we believe are the favorable aspects of its physiologic profile and feel that the available data supports this conclusion.

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Footnote

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References

