Editorial

Etomidate: to use or not to use for endotracheal intubation in the critically ill?

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Abstract: Endotracheal intubation is frequently performed in the intensive care unit (ICU). It can be life-saving for many patients who present with acute respiratory distress. However, it is equally associated with complications that may lead to unwanted effects in this patient population. According to the literature, the rate of complications associated with endotracheal intubation is much higher in an environment such as the ICU as compared to other, more controlled environments (i.e., operating room). Thus, the conduct of performing such a procedure needs to be accomplished with the utmost care. To facilitate establishment of the breathing tube, sedation is routinely administered. Given the tenuous hemodynamic status of the critically ill, etomidate was frequently chosen to blunt further decreases in blood pressure and/or heart rate. Recently however, reports have demonstrated a possible association with the use of etomidate for endotracheal intubation and mortality in the critically ill. In addition, this association seems to be predominantly in patients diagnosed with sepsis. As a result, some have advocated against the use of this medication in septic patients. Due to the negative associations identified with etomidate and mortality, several investigators have evaluated potential alternatives to this solution (e.g., ketamine and ketamine-propofol admixture). These studies have shown promise. However, despite the evidence against using etomidate for endotracheal intubation, other studies have demonstrated no such association. This leaves the critical care clinician with uncertainty regarding the best sedative to administer in this patient population. The following editorial discusses current evidence regarding etomidate use for endotracheal intubation and mortality. In particular, we highlight a recent article with the largest population to date that found no association between etomidate and mortality in the critically ill and illustrate important findings that the reader should be aware of regarding this article.

Keywords: Endotracheal intubation; etomidate; intensive care unit (ICU); mortality; sepsis

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Endotracheal intubation in the intensive care unit (ICU) is a common procedure with an estimated incidence of 69% according to one report (1). Routinely, sedation is provided during this procedure to facilitate placement of the endotracheal tube. However, the best way to achieve this task has been questioned in recent years, especially in patients with tenuous hemodynamics (e.g., patients with sepsis and other types of shock). To make matters worse, the rate of hemodynamic perturbations associated with endotracheal intubation in the ICU is much higher than if the procedure is carried out in the operating room (2).

Etomidate is reported to maintain hemodynamics better than other induction agents and is frequently administered for endotracheal intubation in the ICU (3). Etomidate is a sedative that produces rapid onset of anesthesia with little effects on both heart rate and blood pressure. It is a derivative of the imidazole group, thus possessing properties similar to alpha 2B agonists which

cause peripheral vasoconstriction contributing to the stable hemodynamic profile of this drug (4). Because of its reported hemodynamic stability, it is frequently used in patients with hemodynamic instability in the ICU.

Recently, the use of etomidate for endotracheal intubation in septic patients has been questioned due to possible associations with increased mortality (5-7). These studies have demonstrated a relative increase in both mortality and adrenal insufficiency. The increase in adrenal insufficiency is particularly important within the subgroup of septic patients in the ICU as these patients frequently have a component of relative adrenal insufficiency that can potentially alter hemodynamics and lead to instability, especially if sedation is administered for a procedure such as endotracheal intubation. However, the link between a relative increase in mortality and etomidate is not fully elucidated currently. Continued compromise of the adrenal axis from etomidate administration could be one possible mechanism for the observed mortality increase in some studies. Interestingly, the association between etomidate and mortality is not restricted to the septic population in the ICU. A recent investigation conducted on surgical patients demonstrated that patients who receive etomidate versus an alternative agent intra-operatively have a higher morbidity and mortality (8). Due the evidence presented above, there are some that question the use of etomidate in the critically ill (9). However, this not endorsed by all providers as several publications have found no effect on mortality after a single bolus dose of etomidate (10-12).

In this issue of CHEST, Gu *et al.* reported on a systematic review and meta-analysis of randomized controlled trials and observational studies which revealed no association between etomidate and mortality, although an association with adrenal insufficiency was demonstrated (13). This study was the largest to date with a sample size of approximately 5,500 patients. Of the included studies, 2 were from randomized controlled trials with 18 coming from observational studies. Both randomized controlled trials found no significant associations with etomidate and mortality. However, these trials, although less likely to introduce bias, enrolled a small number patients. The observational studies on the other hand were larger with conflicting results among the individual studies. However, these studies are prone to greater biases than their counterparts. One should note that although the present meta-analysis did not find significant associations with mortality, there was trend toward increased mortality with etomidate use [RR 1.20 (0.84-1.72) for the randomized controlled trials and RR 1.05 (0.97-1.13) for the observational studies]. Evaluating the two different study designs, one can conclude that the mortality increase is likely less than 20% and possibly closer to 5% as indicated by the confidence intervals. Using 5% as the absolute risk increase, the number need to harm, if using etomidate in the critically ill, corresponds to a number needed to harm of approximately 20. This may be an unacceptable risk to critical care providers who encounter this population frequently. Solutions to this potential problem have recently been evaluated. For example, Jabre *et al.* demonstrated that ketamine administered in the pre-hospital setting is a safe and valuable alternative to etomidate (14). In addition, a study evaluating ketamine-propofol admixture ("ketofol") versus etomidate among the critically ill is currently under investigation (15).

Although we have not found conclusive evidence that etomidate increases mortality in critically ill patients, it does appear to increase the risk of adrenal insufficiency thereby possibly contributing to multi-organ system dysfunction according to a recent study (16). The clinical implications of this have yet to be determined. Regardless, when faced with a patient in acute respiratory distress who has a precious hemodynamic status, establishment of the breathing tube can be accomplished by alternative means [e.g., ketamine and possibly ketamine-propofol admixture ("ketofol")] (14,17,18). Until more is known about the potential risks of etomidate, the clinician should be aware of these alternatives in an effort to maximize benefit for critically ill patients.

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Footnote

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