Etomidate is associated with mortality and adrenal insufficiency in sepsis: A meta-analysis*

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Objective: To evaluate the effects of single-dose etomidate on the adrenal axis and mortality in patients with severe sepsis and septic shock.

Design: A systematic review of randomized controlled trials and observational studies with meta-analysis.

Setting: Literature search of EMBASE, Medline, Cochrane Database, and Evidence-Based Medical Reviews.

Subjects: Sepsis patients who received etomidate for rapid sequence intubation.

Interventions: None.

Measurements and Main Results: We conducted a systematic review of randomized controlled trials and observational studies with meta-analysis assessing the effects of etomidate on adrenal insufficiency and all-cause mortality published between January 1950 and February 2012. We only examined studies including septic patients. All-cause mortality served as our primary end point, whereas the prevalence of adrenal insufficiency was our secondary end point. Adrenal insufficiency was determined using a cosyntropin stimulation test in all studies. We used a random effects model for analysis; heterogeneity was assessed with the $I^2$ statistic. Publication bias was evaluated with Begg’s test. Five studies were identified that assessed mortality in those who received etomidate. A total of 865 subjects were included. Subjects who received etomidate were more likely to die (pooled relative risk 1.20; 95% confidence interval 1.02–1.42; Q statistic, 4.20; $F$ statistic, 4.9%). Seven studies addressed the development of adrenal suppression associated with the administration of etomidate; 1,303 subjects were included. Etomidate administration increased the likelihood of developing adrenal insufficiency (pooled relative risk 1.33; 95% confidence interval 1.22–1.46; $Q$ statistic, 10.7; $F$ statistic, 43.9%).

Conclusions: Administration of etomidate for rapid sequence intubation is associated with higher rates of adrenal insufficiency and mortality in patients with sepsis. (Crit Care Med 2012; 40:2945–2953)

Key Words: adrenal insufficiency; etomidate; meta-analysis; mortality; sepsis; septic shock

The use of etomidate for rapid sequence intubation remains controversial, particularly in patients with sepsis and septic shock. Initially developed as a continuous infusion for sedation, etomidate was later found to cause prolonged adrenal insufficiency (AI) and resulted in increased mortality (1, 2). Although unsafe for use for sedation in mechanically ventilated patients, physicians began using it in a single-dose administration approach to facilitate endotracheal intubation. Its rapid onset of action along with its minimal effect on cardiovascular and pulmonary parameters made it appear to be an ideal induction agent (3). However, even after one dose, etomidate inhibits adrenal mitochondrial 11-β-hydroxylase activity and may induce adrenal suppression (4). In those suffering severe sepsis/septic shock, and who therefore face an increased risk of AI, this effect may be particularly pronounced.

Multiple clinical trials have demonstrated etomidate’s ability to cause AI in sepsis. In a randomized controlled trial comparing etomidate vs. ketamine for rapid sequence induction, Jabre et al (5) found that subjects who received etomidate were 6.7 times more likely to experience adrenal suppression compared to their ketamine-treated counterparts. This was subsequently confirmed in an a priori subgroup analysis of the Corticosteroid Therapy of Septic Shock trial where 61% of participants did not respond to cosyntropin after exposure to etomidate as opposed to 44.6% ($p = .004$) of those administered another induction agent (6). Despite this confirmation of a connection between etomidate exposure and AI, evidence that precipitating AI via the use of etomidate in septic patients actually increases mortality is lacking. As a result, many continue to debate questions of etomidate’s administration for induction. Thus far, studies performed to address the issue of etomidate and mortality in sepsis have been limited because of their relatively small sample sizes. This has precluded the ability to definitively establish if etomidate increases mortality.

We hypothesized that the use of etomidate during rapid sequence intubation heightens the risk of death and induces AI in patients requiring mechanical ventilation for sepsis. To address our hypothesis, we performed a systematic review of studies of etomidate for use in septic patients for sedation during intubation.

MATERIALS AND METHODS

Data Sources and Search. We conducted a systematic review with meta-analysis of studies between January 1950 and February 2012...
using EMBASE, Medline, Cochrane Database, and all Evidence-Based Medical Reviews. Unpublished data sets such as ClinicalTrials.gov were also searched for ongoing studies. The following keywords were used: etomidate, sepsis, septic shock, severe sepsis, intubation, rapid sequence intubation, sedation, anesthesia, adrenal insufficiency, mortality, and death. There was no restriction to language. Both keywords and Medical Subject Headings were used in a Boolean search strategy. A sample search strategy can be found in the Appendix I. In addition, we conducted manual searches of bibliographies of original articles and abstracts. Approval from the Institutional Review Board was unnecessary because this is a meta-analysis.

Selection of Studies. To evaluate for mortality, we included studies if they met the following criteria: 1) used a randomized or prospective observational approach while evaluating etomidate in sepsis, 2) performed comparisons with a control group, and 3) provided sufficient quantitative data to evaluate mortality (either in-hospital or 28-day) as an outcome.

In contrast, for AI, studies were included if they 1) objectively evaluated for the presence of AI (formal cosyntropin stimulation test or measurement of random cortisol level with a value ≤15 μg/dL), 2) performed comparisons with a control group, and 3) provided quantitative data. We examined both retrospective and prospective studies because fewer external factors affect the development of AI and objective testing for the presence of AI confirmed its diagnosis. For example, in subjects with sepsis or septic shock, only few causes could result in AI: the sepsis itself, the potential use of etomidate, or concomitant adrenal gland dysfunction. Contrarily, because many confounding factors can affect mortality, and yet are difficult to account for in a retrospective study, only prospective studies were included for our assessment of this outcome. Potential confounding variables that are rarely even described in retrospective reports include, but are not limited to, timing and appropriateness of antibiotic therapy, timeliness of resuscitation, comorbid conditions, end-of-life wishes, and family discussions regarding goals of care.

Eligible articles were reviewed by two reviewers for inclusion; disagreements were resolved via discussion. Of the articles considered for inclusion, only two studies required further discussion due to disagreement (7, 8). Both studies were ultimately excluded: one because it was a retrospective review assessing the risk of death after etomidate administration and one because it was duplicate information in abstract form of another included study. When necessary, corresponding authors were electronically contacted to clarify study outcomes. Furthermore, studies were excluded if they were pediatric studies, only published in abstract form as quality of these studies could not be assessed (9), if it was a descriptive study, and if they lacked a control group.

Data Extraction and Outcome Measures. Two reviewers independently extracted data using a standardized data extraction form. From each study, the data abstracted included study design (prospective observational, randomized controlled trial), year of publication, patient demographics (age and gender), and sample sizes for the control and intervention groups. Data regarding severity of illness were also extracted. Severity of illness scoring was obtained based on the scoring system used by the individual study. Finally, we assessed the all-cause mortality rate between groups as our primary outcome measure and the development of AI as our secondary outcome.

Quality Assessment Criteria. Studies that met inclusion criteria were evaluated for quality using the modified Jadad scale (10). The presence of the following six features were appraised: a description of whether the study was randomized, a description of study blindness, the completeness of the follow-up, a clear description of the inclusion and exclusion criteria, a description of the statistical analysis, and whether adverse effects were assessed. Two raters independently determined quality of the studies included (k = 0.915; 95% confidence interval [CI] 0.821–1.00). For purposes of analysis, disagreements were resolved by consensus.

Statistical Analysis. Outcome data for mortality and AI were summarized using descriptive statistics (simple count and proportions). Meta-analyses were conducted using the fixed effects model when heterogeneity between studies was low (F < 50%) and random effects model otherwise. Between-study heterogeneity was evaluated visually using the Galbraith plot (11) and statistically with the meta-analysis performed using a statistical software package (Stata, version 10; StataCorp, College Station, TX).

RESULTS

Based on the initial search, 106 articles were evaluated independently by at least two reviewers and 48 were immediately excluded. A total of 58 potential studies were identified in our literature search. We excluded 48 studies, leaving ten studies (5, 14–22) (Fig. 1). These ten studies reported on 1,623 patients with sepsis or septic shock. Of these ten studies, seven evaluated mortality (5, 14–18, 22) and seven assessed the development of AI (5, 14, 15, 18–21) (four studies assessed both). Of the ten studies included for meta-analysis, five studies included data from randomized controlled trials (5, 14, 16, 20, 22), two were prospective observational studies (17, 21), and three were retrospective observational studies (15, 18, 19). Only five prospective studies were
Criteria were described in eight studies (100%), but the inclusion and exclusion was adequately described in all ten studies for subjects enrolled. Statistical analysis were blinded and had adequate follow-up the five randomized controlled studies. Jadad score was 5.5 (range, 4–7). Four of randomized controlled trials, the average quality. Of the data obtained from sepsis (5).

One of these five studies compared etomidate with ketamine (5) and another compared etomidate with midazolam as an induction agent (16). All studies included in the mortality analysis reported on vital status at discharge. However, only three additionally described 28-day mortality (5, 14, 22).

Of the seven studies used to determine the effects of etomidate on the adrenal axis, all studies used a cosyntropin stimulation test, which was defined as a ≤9 μg/dL rise in serum cortisol level of ≤5 μg/dL to define the presence of AI (15). One prospective study compared the use of etomidate vs. ketamine in 234 subjects but only 76 participants had sepsis (5).

Most of the studies reviewed had limited quality. Of the data obtained from randomized controlled trials, the average Jadad score was 5.5 (range, 4–7). Four of the five randomized controlled studies were blinded and had adequate follow-up for subjects enrolled. Statistical analysis was adequately described in all ten studies (100%), but the inclusion and exclusion criteria were described in eight studies (80.0%). Finally, only one study failed to assess adverse events.

Mortality. The results of the pooled relative risks (RRs) are given in Table 1 and Figure 2. The five studies included in the mortality analysis enrolled 865 septic patients. Only one of these five studies demonstrated an association between mortality and the use of etomidate. When pooled, there was a statistically significant higher risk of death associated with etomidate use for rapid sequence intubation (pooled RR 1.20; 95% CI 1.02–1.42; Q statistic, 4.20; F statistic, 4.99%). Because many variables affect mortality, we conducted a sensitivity analysis using only data collected from the randomized controlled trials. Despite a now smaller sample size to analyze (n = 759), etomidate remained associated with a higher risk of death in septic patients requiring rapid sequence intubation (pooled RR 1.26; 95% CI 1.06–1.50; Q statistic, 3.39; F statistic, 11.6%). Finally, because the time point for assessing mortality differed between studies, we conducted a further sensitivity analysis pooling the data from three randomized controlled trials focused only on 28-day mortality. Of the 637 total subjects, there was still a significantly higher risk of death in individuals exposed to etomidate (pooled RR 1.28; 95% CI 1.06–1.54; Q statistic, 3.70; F statistic, 46.0%). There was no evidence of publication bias (p = 1.000 for the Begg’s test). After using the trim and fill method, these results did not change when all studies were included in the analysis but differed in the latter two sensitivity analyses (Fig. 3). The pooled RR for mortality of all five studies was 1.16 (95% CI 1.02–1.29; Q statistic, 5.11; p = .276) after the fill and trim methodology and was 1.10 (95% CI 0.97–1.22; Q statistic, 9.89; p = .078) for data obtained from randomized controlled trials. In the studies that assessed 28-day mortality, the new pooled RR was 1.08 (95% CI 0.95–1.21; Q statistic, 10.83; p = .028).

Adrenal Insufficiency. The studies used to determine whether etomidate is associated with AI are described in Table 2 and Figure 4. Seven studies were included for analysis yielding a total of 1,303 subjects. Three studies were randomized controlled trials, three were retrospective studies, and one was a prospective study. Of these, five concluded that etomidate is associated with the development of relative AI whereas two did not. All except two studies directly compared the effects of etomidate and alternative anesthetics on the adrenocortical axis. The primary end point for the two remaining studies

<table>
<thead>
<tr>
<th>Study/Year (Country-Language)</th>
<th>Intervention</th>
<th>Design</th>
<th>Age, yrs*</th>
<th>Male Gender, %</th>
<th>Severity of Illness (Score)*</th>
<th>End Point</th>
<th>Mortality in Etomidate Group, n (%)</th>
<th>Mortality in Comparison Group, n (%)</th>
<th>Quality Score</th>
<th>Quality Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuthbertson et al/2009 (14) (Israel-English)</td>
<td>Etomidate (any dose) vs. other sedatives</td>
<td>Subgroup of double-blind RCT</td>
<td>65 [57–74]</td>
<td>499</td>
<td>66.5</td>
<td>SAPS II (48 [37–62])</td>
<td>All-cause mortality</td>
<td>41 (42.7)</td>
<td>123 (30.5)</td>
<td>4</td>
</tr>
<tr>
<td>Tekwani et al/2009 (17) (USA-English)</td>
<td>Etomidate vs. other sedatives</td>
<td>Prospective observational cohort</td>
<td>77 [68–84]</td>
<td>106</td>
<td>45.3</td>
<td>Mortality in the Emergency Department of Sepsis (13 [10–16])</td>
<td>All-cause mortality</td>
<td>28 (38.0)</td>
<td>14 (43.7)</td>
<td>1</td>
</tr>
<tr>
<td>Jabre et al/2009 (5) (French-English)</td>
<td>Etomidate (0.3 mg/kg) vs. ketamine (2 mg/kg)</td>
<td>Single-blind RCT</td>
<td>57.9 ± 18.6</td>
<td>76</td>
<td>59.7</td>
<td>SAPS II (50.9 ± 17.9)</td>
<td>All-cause mortality</td>
<td>17 (41.5)</td>
<td>12 (34.3)</td>
<td>5</td>
</tr>
<tr>
<td>Tekwani et al/2010 (16) (USA-English)</td>
<td>Etomidate (0.3 mg/kg) vs. midazolam (0.1 mg/kg)</td>
<td>Double-blind RCT</td>
<td>72 [60–82]</td>
<td>122</td>
<td>22.1</td>
<td>SAPS II (54 ± 16)</td>
<td>All-cause mortality</td>
<td>26 (36)</td>
<td>21 (43)</td>
<td>7</td>
</tr>
<tr>
<td>Cherfan et al/2011 (22) (Saudi Arabia-English)</td>
<td>Etomidate (20 mg) vs. other sedatives</td>
<td>Subgroup of double-blind RCT</td>
<td>61.0 ± 12.0</td>
<td>62</td>
<td>59.7</td>
<td>Sequential Organ Failure Assessment (15.2 ± 3.3)</td>
<td>All-cause mortality</td>
<td>21 (91)</td>
<td>33 (84)</td>
<td>6</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; SAPS, Simplified Acute Physiology Score.

*Either mean ± SD or median [interquartile range].
evaluated the effect of corticosteroids on patients with sepsis. Collectively, the seven studies confirmed the association between etomidate and the presence of AI in patients with sepsis (pooled RR 1.33; 95% CI 1.22–1.46; Q statistic, 10.7; F statistic, 0.0%). Publication bias was not seen ($p = .23$ using the Begg’s test). These findings did not change after the trim and fill method (Fig. 5). The pooled RR remained unchanged: 1.34 (95% CI 1.26–1.42; Q statistic, 21.0; $p = .004$) when including all studies and 1.33 (95% CI 1.25–1.41; Q statistic, 6.37; $p = .173$) for data collected from randomized controlled trials. We did not perform a metaregression analysis to evaluate whether the presence of AI was associated with increased mortality because only two studies examined the effect of etomidate on both AI and mortality; there were insufficient observations to properly assess this relationship. One study determined that there was no association between the development of AI and mortality, whereas the other study did not comment on this relationship.

**DISCUSSION**

Thus far, few studies have assessed the mortality effects of single-dose etomidate on patients with sepsis or septic shock. Its convenient administration with minimal hemodynamic and pulmonary side effects makes it an appealing drug to assist with rapid sequence intubation. However, its long-term effects have not been well evaluated. This meta-analysis found that the use of etomidate as a sedative for intubation in patients with sepsis is associated with increased rates of AI and mortality. In this patient population, the risk of death was 1.20 times higher for those exposed to etomidate compared to other sedatives. This relationship persisted whether one examined all prospective analyses or only data obtained from formal RCTs.

Our findings confirm the results of a prior meta-analysis looking at the effects of etomidate and mortality in critically ill patients (23). In their review, etomidate was associated with higher rates of AI (pooled RR 1.64; 95% CI 1.52–1.77; $p < .0001$) and death (pooled RR 1.19; 95% CI 1.10–1.30; $p < .0001$). In their subgroup analysis of patients
with sepsis, they also found increased rates of mortality among the etomidate group compared to alternative sedatives (pooled RR 1.22; 95% CI 1.11–1.35; I² = 74%). The results of our study add to this prior literature and are novel in that we chose to include studies that only evaluated mortality prospectively and decided to assess the effect of etomidate on a specific disease causing critical illness. We also included data published since this prior meta-analysis. Because a multitude of factors (e.g., pressor requirement, fluid management, patient choice, end-of-life discussions, severity of illness, and etiology of critical illness) affect mortality, particularly in the critically ill, we decided to limit the present meta-analysis so as to include only prospective studies to attempt to minimize these potential confounding factors. Furthermore, sensitivity analyses were performed on only RCTs to confirm the presence of a mortality penalty for those with sepsis exposed to etomidate. The benefit of including only RCTs is the ability to control to some degree for the confounding effects of the aforementioned confounders.

The results from this meta-analysis, particularly in light of earlier reports, are concerning. It suggests that even single-dose etomidate can potentially cause harm in patients with sepsis or septic shock. Prior evidence established that continuous infusion etomidate increased mortality rates due to its ability to suppress the adrenal axis (24, 25). In this sense our meta-analysis is novel, as noted earlier, in that we specifically focus on the current approach to etomidate administration and similarly address the question of etomidate’s safety in a homogeneous group at high risk for relative AI. More importantly, however, given that those with severe sepsis and septic shock already face high rates of death, avoiding actions that potentially increase the risk for mortality represents an overriding concern.

Our findings suggest that clinicians should be more cautious when using etomidate to induce sedation, particularly in patients with sepsis or septic shock. The present meta-analysis serves to help illustrate an issue physicians must consider relative to etomidate use and suggest that rather than routine use there is a need for an approach that expressly balances risks and benefits. Specifically, we do not advocate complete cessation of etomidate’s use based on this meta-analysis. Rather, we suggest that there is now sufficient evidence to warrant a more thoughtful approach to its application. Certainly, the inability of this study to demonstrate a clear relationship between the development of AI and mortality leads to skepticism about the results. The mortality risk noted adds to the dilemma regarding the effects of AI in sepsis. Although prior evidence demonstrated that AI significantly affects prognosis, the recent Corticosteroid Therapy
of Septic Shock trial was unable to confirm that treatment with physiologic doses of steroids actually improves outcomes in patients with severe sepsis (6). Furthermore, although all studies used the same criteria to describe relative AI, this definition has never been proven to truly represent a clinically significant loss in adrenal function (26). Thus, identifying a biologically plausible relationship between AI and mortality is paramount to understanding the true risks associated with administering etomidate to patients with sepsis.

In a recent randomized controlled trial enrolling 99 nonseptic critically ill patients given single-dose etomidate, nearly 90% of subjects developed AI (27). Identifying this high prevalence of etomidate-related AI in critically ill patients without sepsis may be the first step to understanding the relationship between etomidate and increased mortality. Indeed, the effects of etomidate-related AI may be more pronounced in septic patients who are potentially predisposed to impairments in adrenal function. The induction of AI has also been recently demonstrated in an animal model of sepsis. Pejo and colleagues (28) measured corticosterone levels in male Sprague-Dawley rats after single and multiple doses of etomidate and a novel pyrrole analog of etomidate, carboetomidate. It was noted that even after single-dose etomidate, cortisone levels decreased and were substantially lower as compared to carboetomidate. More importantly, however, this study establishes that carboetomidate may be a promising new sedative for patients with sepsis.

This meta-analysis also demonstrates that the quality of literature investigating etomidate in severe sepsis and septic shock is limited in both quantitative and qualitative fashions. For example, despite etomidate’s frequent use, only 11 studies evaluated the development of AI and/or mortality. Of these, only five were prospective studies. In fact, to increase the robustness of the sample, we...
included two studies that did not primarily assess the effects of etomidate on AI and mortality but rather assessed the use of steroids in sepsis (20, 21). As a consequence, data from these studies could only be used to analyze the effects of etomidate on AI. Some of the subjects in the etomidate group in each study would have received corticosteroids, which may either directly affect mortality in sepsis or potentially “rescue” a patient from etomidate-related AI. This necessarily introduces a significant potential confounder for determining mortality and any potential causative relationship between etomidate and mortality. Further illustrating the limited quantity and quality of available studies regarding this topic is reflected in the results obtained from the trim and fill method for assessing the presence of publication bias. The fact that the mortality outcome differed significantly using this method demonstrates the possibility that publication bias exists. The paucity of evidence evaluating the safety profile of a single dose of this drug despite prior evidence of its potential for harm is worrisome. It would appear that physicians committed the logical fallacy of concluding that the absence of proof of harm with short-term use of etomidate implied there was proof of the absence of such danger. The majority of the studies assessing etomidate administration for rapid sequence induction were underpowered to truly assess the relationship between single-dose etomidate and either the development of relative AI or mortality. Therefore, prior conclusions that the use of etomidate for sedation is benign and that it does not increase the risk of death may simply be due to issues with sample size rather than the true exclusion of an association between etomidate and death. Similar to other drugs, this new information about etomidate’s potential for harm should cause us to reevaluate the use of this drug and is a stepping stone to realizing future research endeavors to clarify this relationship. For example, the use of etomidate can be likened to that of long-acting beta agonists for asthma. Potential harm associated with the administration of long-acting beta agonists was not originally suggested in the initial trials of these agents. However, these initial studies which resulted in regulatory approval were small and had only short-term follow-up. Only when long-term trials emerged did a concern arise. Presently, the Food and Drug Administration has mandated multiple clinical trials further assessing the reality of this harm. Given the parallels between the scenario surrounding long-acting beta agonist use and etomidate use, it seems prudent to require that etomidate be subjected to the same rigorous evaluation to clarify the nexus among etomidate, AI, and mortality.

Our study has several limitations. As is the case with all meta-analyses, the results of this study are dependent on the quality and quantity of studies included in the analysis. Despite the lack of heterogeneity between studies, the individual studies varied substantially. They varied from the type of comparative sedative, to the severity of illness score used, to the timing used to determine the presence of AI. While the $I^2$ statistic is an indicator for data consistency, it does not account for differences within studies (29). The small number of randomized trials available for inclusion illustrates the lack of quality data assessing the utility of etomidate for intubation. Furthermore, individually, each of the randomized trials had flaws that could have significantly influenced our findings: two studies were performed as subgroup analyses and were therefore subject to measurement bias, whereas the other two randomized trials had small sample sizes. In our data search, only two studies assessed both the effects of single-dose etomidate on adrenal function and mortality, which precluded us from determining the true relationship between AI and mortality in this patient population. We attempted to increase the sample size by evaluating etomidate studies in critically ill subjects and extracting data on septic patients but found insufficient data to improve the robustness of our data set. In addition, all-cause mortality is affected by multiple factors including severity of illness,
cause of illness, and timely appropriate administration of antimicrobials. In this case, the increased mortality noted could also be due to selection bias where those who received etomidate were less stable hemodynamically or were more difficult to intubate and therefore required etomidate as a part of rapid sequence intubation. Due to the impact of these potential factors, we restricted our inclusion criteria to prospective studies. We further repeated the analysis using only data from randomized controlled trials to minimize potential confounding factors and to curtail the effects of selection bias. This was only partially accomplished, though, as the entire cohort of subjects from these randomized controlled trials were not included in the analysis. In the study by Jabre et al (5), we only incorporated data regarding patients with sepsis while subjects for the study by Cuthbertson et al (14) were truly randomized to hydrocortisone vs. placebo and not etomidate vs. alternative sedatives. Regardless, we performed sensitivity analyses to more specifically examine whether there exists a mortality penalty associated with etomidate by using data obtained from the most robust form of clinical trial, the randomized controlled trial. Another potential limitation is the inability to differentiate the etiology for AI. Certainly, AI could be drug related, sepsis related, or due to pathologic disease (e.g., adrenalitis), although the likelihood of non-drug-related disease is small given the types of patients evaluated and the fact that randomization ought to have balanced the risk for non-drug-related AI between the control and intervention cohorts. Finally, the primary outcome of mortality differed between the studies pooled. In two of the randomized controlled trials, the mortality end point was assessed at 28 days, whereas in the other two studies in-hospital mortality was evaluated. These varying definitions complicated the ability to uniformly pool these studies. Nevertheless, irrespective of the definition for mortality, the use of single-dose etomidate was still associated with higher mortality rates.

CONCLUSIONS

In conclusion, our meta-analysis suggests that even one-time administration of etomidate can result in AI. More importantly, single-dose etomidate may be associated with all-cause mortality in those with severe sepsis/septic shock. While there are significant limitations to this meta-analysis, our findings indicate that clinicians must be more selective about administering etomidate to facilitate sedation for intubation. Most importantly, this study emphasizes the need for a randomized controlled trial to evaluate the safety profile of single-dose etomidate as a general anesthetic. The high prevalence of its use may be associated with significant healthcare implications if the broad use of this drug continues uninvestigated. Finally, the results of this meta-analysis can be used to generate the specific hypotheses and sample size calculations to guide future research projects.

REFERENCES


APPENDIX 1: SEARCH STRATEGY FOR MEDLINE

1. Search “etomidate” [MeSH]
2. Search “etomidate” [tw]
3. Search 1 OR 2
4. Search “sedation” [tw]
5. Search “procedural sedation” [tw]
6. Search “anesthesia” [MeSH]
7. Search “anesthesia” [tw]
8. Search “intubation” [MeSH]
9. Search “intubation” [tw]
10. Search “intubation, intratracheal” [MeSH]
11. Search “intubation, intratracheal” [tw]
12. Search “rapid sequence intubation” [tw]
13. Search 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. Search “mortality” [MeSH]
15. Search “mortality” [tw]
16. Search “death” [MeSH]
17. Search “death” [tw]
18. Search 14 OR 15 OR 16 OR 17
19. Search “adrenal insufficiency” [MeSH]
20. Search “adrenal insufficiency” [tw]
21. Search 19 OR 20
22. Search “sepsis” [MeSH]
23. Search “sepsis” [tw]
24. Search “severe sepsis” [tw]
25. Search “shock, septic” [MeSH]
26. Search “septic shock” [tw]
27. Search “septic” [tw]
28. Search 22 OR 23 OR 24 OR 25 OR 26 OR 27
29. Search 13 AND 18 AND 28
30. Search 13 AND 21 AND 28