Etomidate: Buy now, pay later?*

Securing the airway is one of the most important task in the early management of critically ill patients. However, endotracheal intubation in emergency settings can lead to serious life-threatening adverse events like pulmonary aspiration and prolonged hypoxia due to failed intubation attempts. To avoid such complications, acute care physicians frequently use rapid sequence intubation, which comprise the simultaneous administration of a rapid-acting hypnotic agent and a neuromuscular blocking agent. However, the administration of nontitrated dose of hypnotic agents in patients with unrecognized hypovolemia and unknown cardiac function may induce postintubation hemodynamic instability, which has been associated with increased in-hospital mortality (1). In this setting, the use of etomidate, a carboxylated imidazole directly blocking the γ-amino butyric acid receptor complex and providing stable hemodynamic conditions (2), appears to be wise.

In this issue of *Critical Care Medicine*, Chan et al (3) evaluated the effect on mortality and adrenal insufficiency of a single dose of etomidate for rapid sequence intubation of patients with sepsis by conducting a systematic review and meta-analysis. The authors observed that etomidate use was associated with an increased risk of adrenal insufficiency (relative risk 1.33, 95% confidence interval 1.22–1.46, seven studies, 1,303 patients) and of 28-day mortality (relative risk 1.20, 95% confidence interval 1.02–1.42, five studies, 865 patients). These findings are concerning because etomidate is the most commonly used hypnotic agent in the emergency room in the United States (4) and may substantially increase the burden of illness related to sepsis, one of the most important reasons of admission in intensive care units (5).

Nevertheless, those results need to be interpreted with great caution. Indeed, systematic reviews are limited by the methodological quality of included studies. Chan et al included data from four randomized controlled trials (RCTs) (6–9) and one prospective cohort study (10) in the meta-analysis on mortality. However, only one RCT directly evaluated the effect of hypnotic agents on mortality in sepsis by randomizing 122 patients to receive either midazolam or etomidate (8). This RCT failed to demonstrate a statistically significant increased of in-hospital mortality (relative risk 1.20, 95% confidence interval 0.76–1.88). Another RCT indirectly compared the effect of etomidate with ketamine in a nonstratified subgroup of 76 patients with sepsis (9). This study also failed to demonstrate any harm of etomidate (relative risk 1.21, 95% confidence interval 0.67–2.17). In the remaining two RCTs evaluating the effect of low-dose glucocorticoid in septic shock, the administration of etomidate was not randomized (6, 7). For the purpose of the research question being asked in this systematic review, those studies should therefore not be considered as RCTs, but as prospective cohort studies. Like the prospective cohort study by Tekwani et al (10), these studies used multivariable logistic regression models to overcome selection bias and adjust for confounding factors. However, the advantages of such adjustment no longer stand in a meta-analysis in which crude data are used.

Etomidate inhibits 11-β-hydroxylase and the conversion of 11-deoxycortisol into cortisol (11). When given in a single-dose bolus, this effect lasts no longer than 48 hrs (12). It was previously suggested that the attributable mortality of etomidate perfusion was due to adrenal insufficiency (13). If true, the association between the administration of a single-dose of etomidate and 28-day mortality is unlikely to be solely related to adrenal insufficiency. Indeed, Cuthbertson et al (7) observed that the attributable effect of etomidate on mortality was independent of glucocorticoid replacement therapy. Also, a recently published RCT of 99 patients without apparent sepsis and intubated with etomidate failed to demonstrate any clinical benefit of glucocorticoid replacement in this setting (14).

By trying to avoid an immediate potentially life-threatening adverse event like postintubation hemodynamic instability, do acute care physicians only postpone complications and cause greater harm? Managing the airway of critically ill patients is complex and associated with significant complications, which cannot be easily avoided and might not just be related to the drugs being used (15). Although important methodological concerns and limitations were highlighted, the study by Chan et al underlines a potential increase in mortality with the use of etomidate for intubation when other alternatives are easily available (9). Given the widespread use of etomidate in the emergency room, we believe that a RCT designed to evaluate the safety of etomidate as a hypnotic agent for endotracheal intubation of patients with sepsis is not only ethical but also urgently warranted.

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***See also p. 2945.**

Key Words: adrenal insufficiency; etomidate; intubation; mortality; sepsis

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The anti-arrhythmic potential of therapeutic hypothermia: Another good reason for keeping your cool?*

In this issue of *Critical Care Medicine*, Piktel and colleagues (1) present data from a canine left ventricular wedge preparation suggesting that therapeutic hypothermia (32–34°C) may be antiarrhythmic during myocardial ischemia. Their data are intriguing, but it is premature to call it compelling. Nevertheless, our grasp of therapeutic hypothermia's benefits remains incomplete, and the history of this treatment modality suggests that intrigue may be enough to result in benefit.

Case reports dating back to 1988 confirm that young children with rectal temperatures ≤25°C survived drowning in icy water without permanent sequelae (2, 3). However, children are thinner than adults and achieve hypothermia more quickly (3). Young patients without comorbidities are also more likely to survive prolonged accidental cardiac arrest following electrocution, and their neurologic recovery may be dramatic (4). Therefore, conclusions about the benefits of hypothermia were difficult to draw from such cases.

Fortunately, these (and other) "miraculous" observations about drowning, hypothermia, and survival spawned hypotheses that cooling could attenuate neurologic damage. Subsequent studies demonstrated that mild or moderate systemic hypothermia clearly reduced brain damage after cardiac arrest in dogs (5).

Two major clinical trials published in 2002 provided direct evidence of neurologic benefit from targeted temperature management in comatose survivors of cardiac arrest. In an Australian trial, the odds ratio for a favorable neurologic recovery with hypothermic vs. normothermic therapy was 5.25 after adjustment for age and duration of arrest (5). A European multicenter trial also reported improved likelihood of a favorable neurologic outcome and significant reduction in the rate of death at 6 months in patients managed with hypothermia (6). These trials became the basis for clinical guidelines on using therapeutic hypothermia in patients after cardiac arrest (5–7). A more recent retrospective study found that therapeutic hypothermia was associated with significantly improved neurological outcome and 180-day survival compared to normothermia in cardiac-arrest patients (8).

Unfortunately, all of this good news does not answer any questions about hypothermia and arrhythmogenesis. As Piktel et al note, severe hypothermia (<30°C) is proarrhythmic and may result in ventricular fibrillation that is refractory to conventional therapy (1, 9, 10). They hypothesize that this may be the result of increased dispersion of refractoriness (1).

In the current study, the authors found that mild hypothermia attenuated ischemia-induced increases in dispersion of refractoriness and reduced

*See also p. 2954.

Key Words: antiarrhythmic; cardiac arrest; conduction delay; dispersion of refractoriness; hypothermia

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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; I^2 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; I^2 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 ven-tilation for sepsis. To address our hypothesis, we performed a systematic review of studies of etomidate for use in septic patients for sedation during initial intubation.

MATERIALS AND METHODS

Data Sources and Search. We conducted a systematic review with meta-analysis of studies between January 1950 and February 2012

***See also p. 3086.**

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Dr. Chan participated in the conception, literature review process, data abstraction, data analysis, and drafting of this manuscript. Dr. Mitchell participated in the literature review process, data abstraction process, and drafting of this manuscript. Dr. Shorr assisted in the conception, data analysis, and drafting of this manuscript.

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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 1. 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 ($\kappa = 0.915$; 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 ($I^2 < 50\%$) and random effects model otherwise. Between-study heterogeneity was evaluated visually using the Galbraith plot (11) and statistically with the I^2 statistic (12). Funnel plots were used to visually assess for publication bias while the methods of Beggs and Berlin (13) were used to statically confirm the presence of publication bias. We further assessed publication bias using the trim and fill method to account for bias due to potentially unpublished negative data. In addition, sensitivity analysis was performed to determine the effects of study quality (e.g., randomized controlled trials) and study type on outcome. Finally, a random effects metaregression was used to adjust for potential differences between studies. All analyses were 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

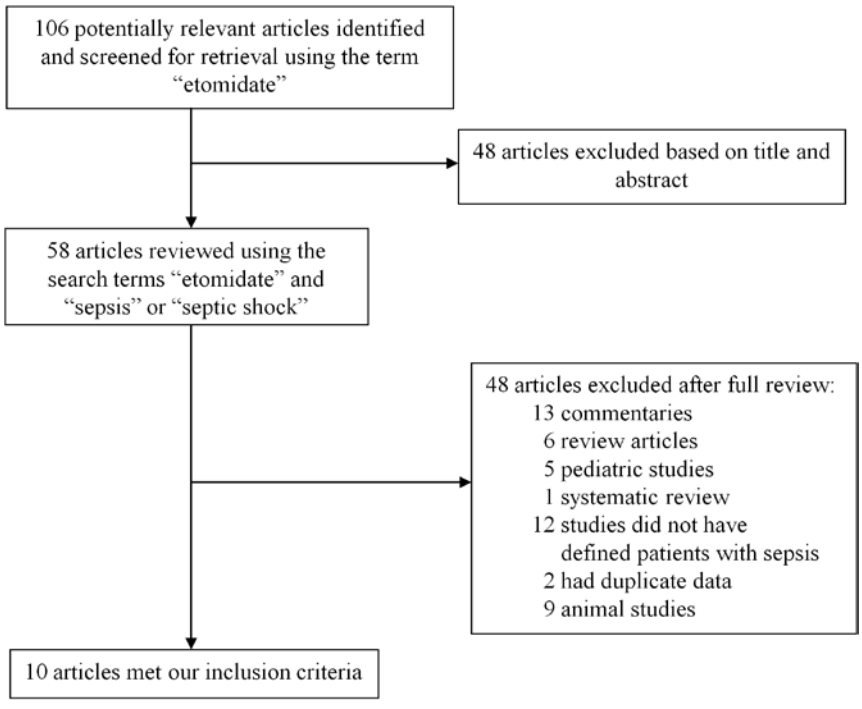

Figure 1. Flowsheet of study selection process.

Table 1. Studies included for mortality

Study/Year (Country-Language)	Intervention	Design	Age, yrs[a]	Patients, n	Male Gender, %	Severity of Illness, (Score)[a]	End Point	Mortality in Etomidate Group, n (%)	Mortality in Comparison Group, n (%)	Quality Score	Quality Problems
Cuthbertson et al/2009 (14) (Israel-English)	Etomidate (any dose) vs. other sedatives	Subgroup of double-blind RCT	65 [57–74]	499	66.5	SAPS II (48 [37–62])	All-cause 28-day mortality	41 (42.7)	123 (30.5)	4	Randomization; blinding
Tekwani et al/2009 (17) (USA-English)	Etomidate vs. other sedatives	Prospective observational cohort	77 [68–84]	106	45.3	Mortality in the Emergency Department of Sepsis (13 [10–16])	All-cause in-hospital mortality	28 (38.0)	14 (43.7)	1	Inclusion/exclusion criteria; follow-up; adverse effects
Jabre et al/2009 (5) (French-English)	Etomidate (0.3 mg/kg) vs. ketamine (2 mg/kg)	Single-blind RCT	57.9 ± 18.6	76	59.7	SAPS II (50.9 ± 17.9)	All-cause 28-day mortality	17 (41.5)	12 (34.3)	5	Follow-up
Tekwani et al/2010 (16) (USA-English)	Etomidate (0.3 mg/kg) vs. midazolam (0.1 mg/kg)	Double-blind RCT	72 [60–82]	122	22.1	SAPS II (54 ± 16)	All-cause in-hospital mortality	26 (36)	21 (43)	7	None
Cherfan et al/2011 (22) (Saudi Arabia-English)	Etomidate (20 mg) vs. other sedatives	Subgroup of double-blind RCT	61.0 ± 12.0	62	59.7	Sequential Organ Failure Assessment (15.2 ± 3.3)	All-cause 28-day mortality	21 (91)	33 (84)	6	Randomization

RCT, randomized controlled trial; SAPS, Simplified Acute Physiology Score.
[a]Either mean ± SD or median [interquartile range].

used to assess mortality (5, 14, 16, 17, 22). One of these five studies compared etomidate specifically 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 30 and/or 60 mins after the administration of 250 μg of cosyntropin. Only one study also used a random cortisol level of ≤15 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; I^2 statistic, 4.9%). 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; I^2 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; I^2 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

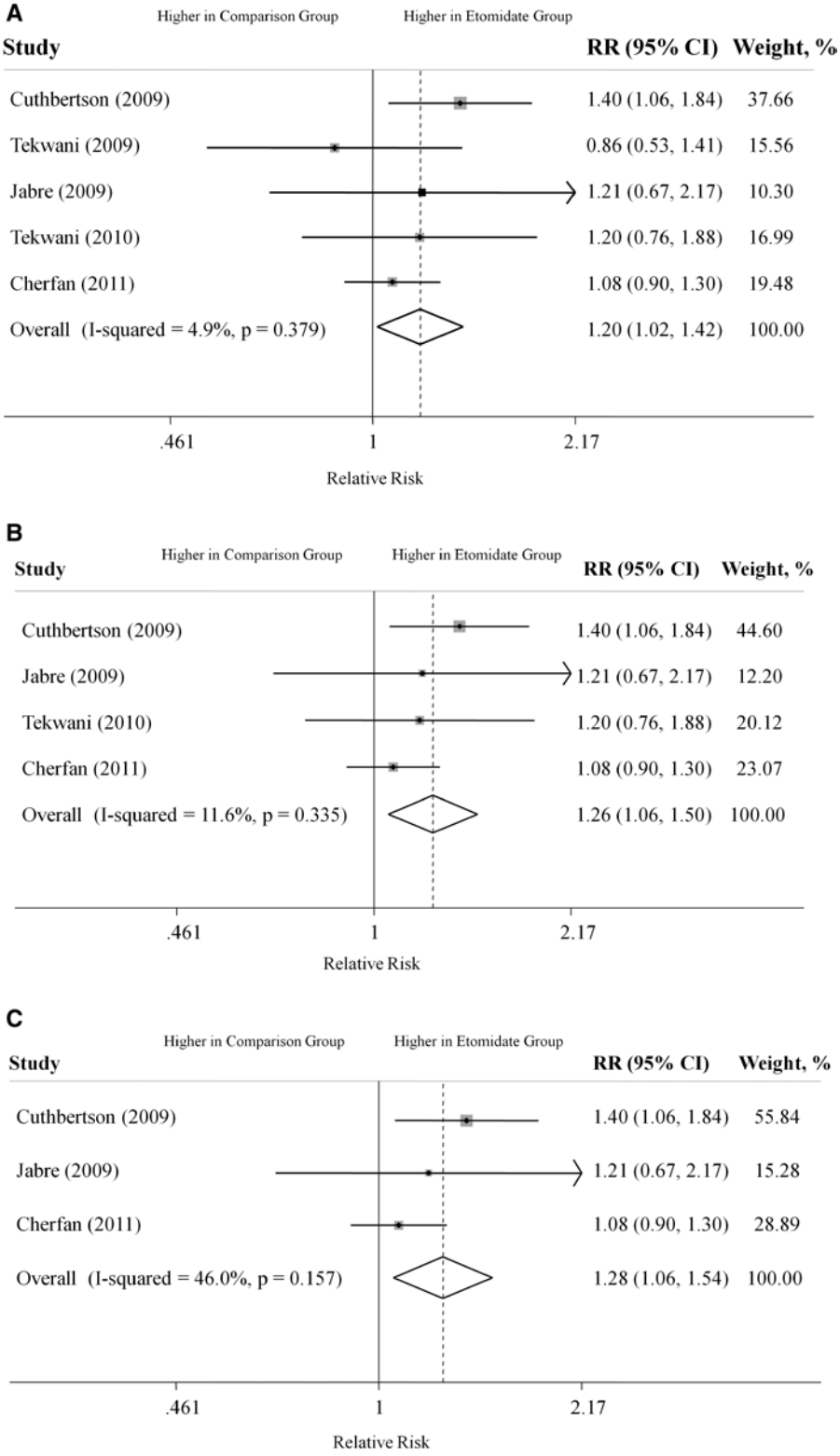

Figure 2. *A*, Pooled relative risks (*RR*s) for all-cause mortality: all studies. *B*, Pooled RR for mortality: randomized controlled trials. *C*, Pooled RR for mortality: 28-day mortality rates only. *CI*, confidence interval.

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; I^2 statistic, 43.9%). To minimize bias associated with retrospective studies, we performed a sensitivity analysis using only data from the randomized controlled trials. Again, despite a reduction in sample size (n = 844), there was a persistence in relative AI associated with the use of etomidate for induction (pooled RR 1.35; 95% CI 1.24–1.47; Q statistic, 1.24; I^2 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 who were exposed to etomidate compared to other sedatives. This relationship persisted when only data from higher quality randomized controlled trials were analyzed (1.26 times higher likelihood of death). In addition, the relationship with AI 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

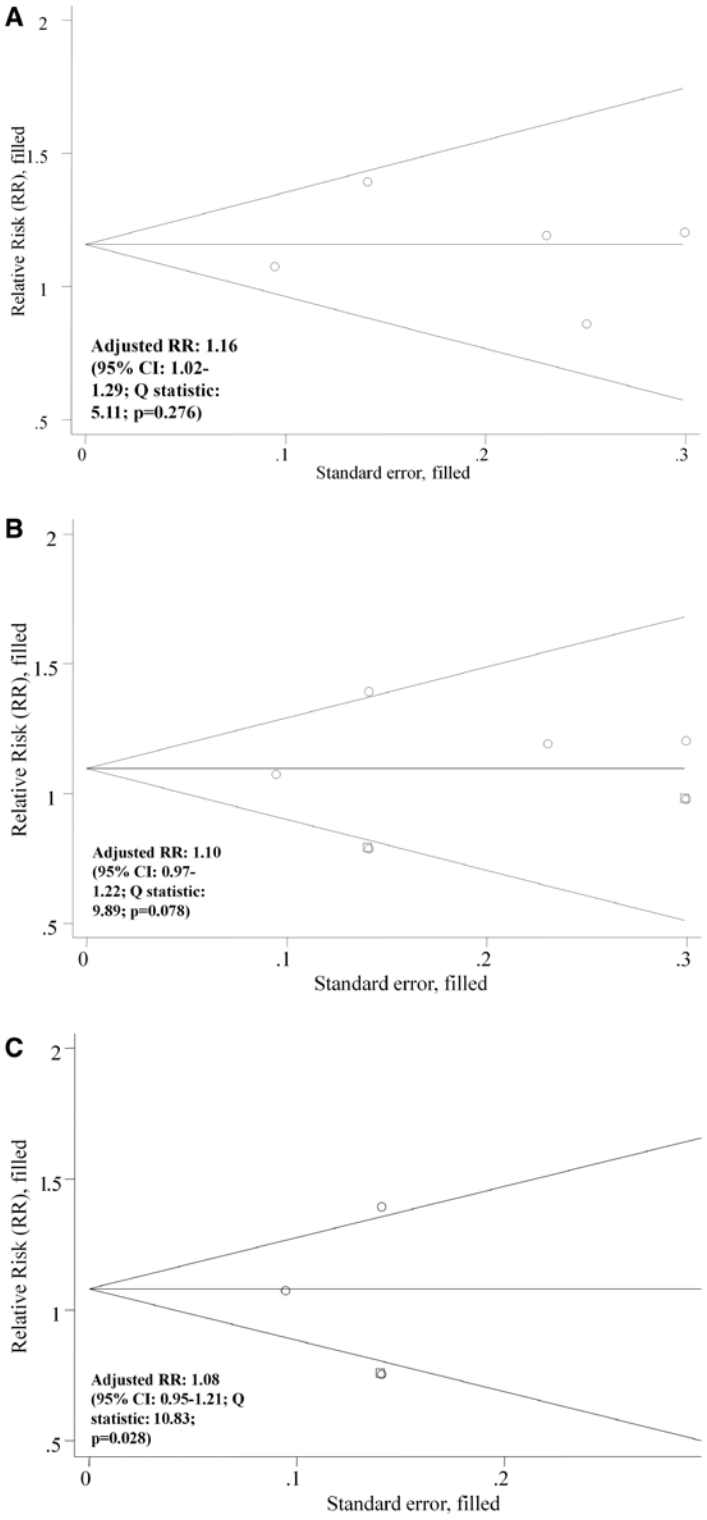

Figure 3. *A*, Filled funnel plot using the trim and fill method for mortality: all studies. *B*, Filled funnel plot using the trim and fill method for mortality: randomized controlled trials. *C*, Filled funnel plot using the trim and fill method for mortality: 28-day mortality. *CI*, confidence interval; *RR*, relative risk.

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; I^2 = 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

Table 2. Studies included for adrenal insufficiency

Study/Year (Country-Language)	Intervention	Design	Age, yrs[a]	Patients, n	Male Gender, %	Severity of Illness (Score)[a]	End Point [Time Frame for AI Testing After Etomidate Dose]	AI in Etomidate Group, n (%)	AI in Comparison Group, n (%)	Quality Score	Quality Problems
Cuthbertson et al/2009 (14) (Israel-English)	Etomidate (any dose) vs. other sedatives	Subgroup of double-blind RCT	65 [57–74]	499	66.5	SAPS II(48 [37–62])	AI by CST (60 mins after 0.25 mg tetracosactrin) [within 72 hrs]	58 (61.0)	175 (44.6)	4	Randomization; blinding
Jabre et al/2009 (5) (French-English)	Etomidate (0.3 mg/kg) vs. ketamine (2 mg/kg)	Single-blind RCT	57.9 ± 18.6	46	59.7	SAPS II(50.9 ± 17.9)	AI by CST (30 and 60 mins after cosyntropin) [within 48 hrs]	21 (80.1)	9 (45.0)	5	Follow-up
Kim et al/2008 (18) (Korean-English)	Etomidate (0.3 mg/kg) vs. midazolam (0.07 mg/kg)	Single-center retrospective cohort	63.6 ± 13.3	65	72.3	Acute Physiology and Chronic Health Evaluation II (27.0 ± 5.9)	AI by CST (0.25 mg tetracosactrin) [within 24 hrs]	21 (84.0)	19 (48.0)	3	Randomization; follow-up
Mohammad et al/2006 (19) (USA-English)	Etomidate vs. other sedatives	Single-center retrospective cohort	60.1 ± 17.3	152	54.6	None	AI by CST (30 and 60 mins after cosyntropin) [at least 24 hrs after etomidate]	29 (76.0)	58 (51.0)	3	Randomization; follow-up
Dmello et al/2010 (15) (USA-English)	Etomidate (0.3 mg/kg) vs. other sedatives	Single-center retrospective cohort	64.5 ± 18.0	126	54.9	Acute Physiology and Chronic Health Evaluation II (21.6 ± 8.2)	AI by CST (30 and 60 mins after 0.25 mg cosyntropin), random cortisol level [within 72 hrs]	16 (24.0)	13 (22.0)	2	Randomization; follow-up; inclusion/exclusion
Annane et al/2002 (20) (French-English)	Etomidate vs. other sedatives	Multicenter blind RCT	61.0 ± 15.5	299	66.9	SAPS II (68.5 ± 19.1)	AI by CST (30 and 60 mins after 0.25 mg tetracosactrin)	68 (94.4)	161 (70.9)	6	Randomization
Riché et al (21)/2007 (French-English)	Etomidate (0.3 mg/kg) vs. other sedatives	Single-center prospective cohort	68.1 ± 15.2	116	61.0	SAPS II (52.0 ± 20.0)	AI by CST (60 mins after 0.25 mg tetracosactrin) [within 24 hrs]	41 (59.4)	30 (63.8)	3	Randomization; follow-up

AI, adrenal insufficiency; RCT, randomized controlled trial; SAPS, Simplified Acute Physiology Score; CST, cortisol stimulation test.
[a]Either mean ± SD or median [interquartile range].

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

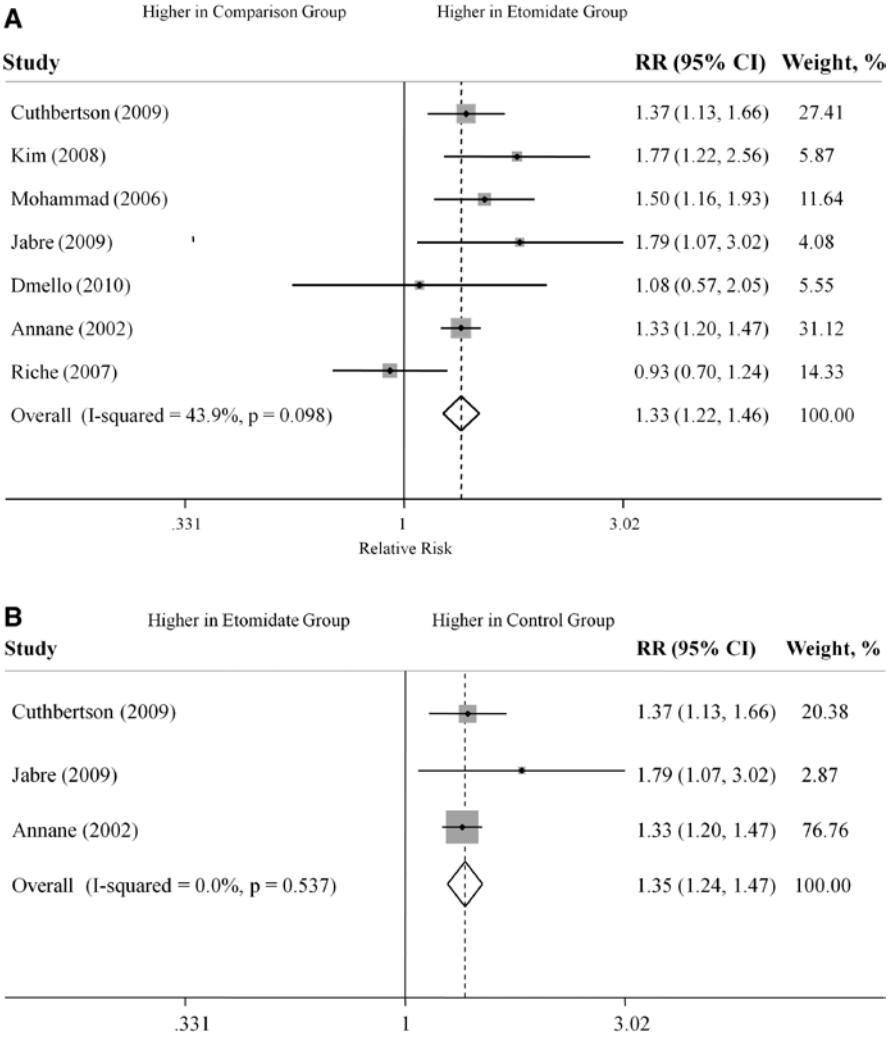

Figure 4. *A*, Pooled relative risk (*RR*) for adrenal insufficiency: all studies. *B*, RR for adrenal insufficiency: randomized controlled trials. *CI*, confidence interval.

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,

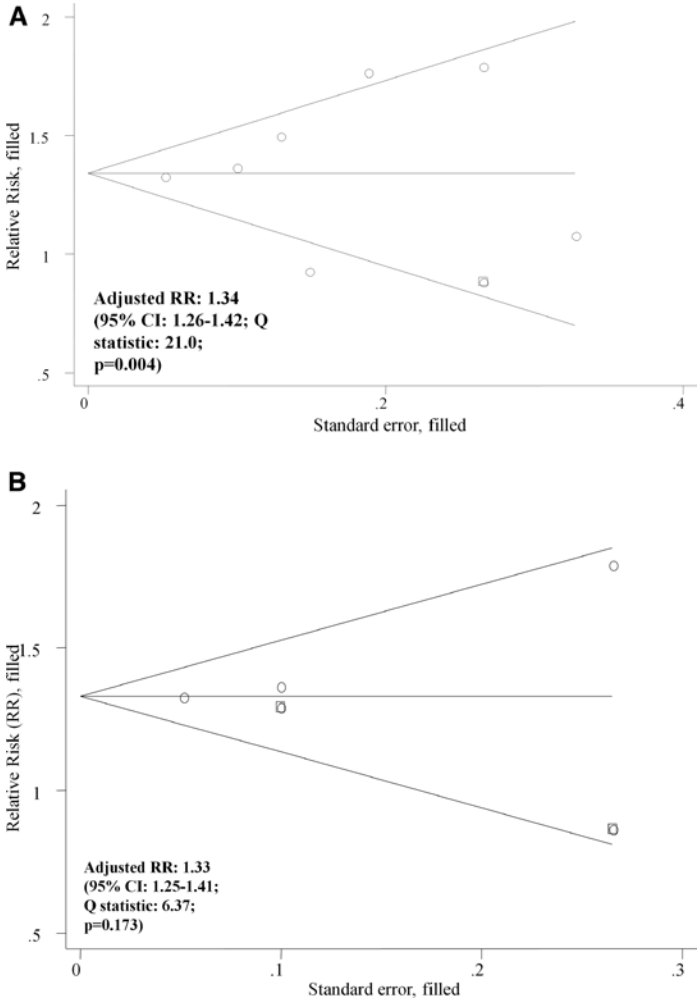

Figure 5. *A*, Filled funnel plot using the trim and fill method for adrenal insufficiency: all studies. *B*, Filled funnel plot using the trim and fill method for adrenal insufficiency: randomized controlled trials. *RR, relative risk; CI, confidence interval.*

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 nondrug-related disease is small given the types of patients evaluated and the fact that randomization ought to have balanced the risk for nondrug-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.

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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