The Effect of a Bolus Dose of Etomidate on Cortisol Levels, Mortality, and Health Services Utilization: A Systematic Review

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Study objective: To synthesize the evidence on the effect of a bolus dose of etomidate on adrenal function, mortality, and health services utilization compared with other induction agents used for rapid sequence intubation.

Methods: We developed a systematic search strategy and applied it to 10 electronic bibliographic databases. We hand searched journals; reviewed conference proceedings, gray literature, and bibliographies of relevant literature; and contacted content experts for studies comparing a bolus dose of etomidate with other induction agents. Retrieved articles were reviewed and data were abstracted with standardized forms. Data were pooled with the random-effects model if at least 4 clinically homogenous studies of the same design reported the same outcome measure. All other data were reported qualitatively.

Results: From 3,083 titles reviewed, 20 met our inclusion criteria. Pooled mean cortisol levels were lower in elective surgical patients induced with etomidate compared with those induced with other agents between 1 and 4 hours postinduction. The differences varied from 6.1 μg/dL (95% confidence interval [CI] 2.4 to 9.9 μg/dL; $P=.001$) to 16.4 μg/dL (95% CI 9.7 to 23.1 μg/dL; $P<.001$). Two studies in critically ill patients reported significantly different cortisol levels up to 7 hours postinduction. None of the studies reviewed, nor our pooled estimate (odds ratio 1.14; 95% CI 0.81 to 1.60), showed a statistically significant effect on mortality. Only one study reported longer ventilator, ICU, and hospital lengths of stay in patients intubated with etomidate.

Conclusion: The available evidence suggests that etomidate suppresses adrenal function transiently without demonstrating a significant effect on mortality. However, no studies to date have been powered to detect a difference in hospital, ventilator, or ICU length of stay or in mortality. [Ann Emerg Med. 2010;56:105-113.]

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INTRODUCTION

Background

Rapid sequence intubation is commonly performed in the emergency department (ED) to secure the airway and initiate mechanical ventilation in critically ill patients.[1] Etomidate has become the most widely used induction agent for this purpose in North America because of its easy dosing profile, hemodynamic tolerance, limited suppression of ventilation, lack of histamine release, and protection from myocardial and cerebral ischemia.[2-9] However, debate about the clinical significance of etomidate's effect on adrenal function has emerged in the critical care and emergency medicine literature after publication of data demonstrating the importance of intact adrenal function for survival in critical illness.[3,10-21]

Importance

The normal response to critical illness is characterized by stimulation of the hypothalamic-pituitary-adrenal axis and results in increased cortisol production.[11,12] Etomidate inhibits this stress response by blocking 11-β hydroxylase. The clinical significance of this effect was first suspected by Ledingham et al, who observed a near doubling of mortality (25% versus 44% mortality; $P<.05$) in a comparable group of intubated trauma patients sedated with etomidate infusions in their ICU.[22] The mortality rate returned to baseline once etomidate infusions were discontinued.[23] Although these data were observational, by the mid-1980s numerous reports had been published that linked etomidate to adrenal insufficiency, and etomidate infusions for continuous sedation were abandoned.[24-39]

Despite lack of definitive data demonstrating the safety of a bolus dose of etomidate for induction of anesthesia and observational studies indicating potential for harm,[18,21,40-42] etomidate continues to be used routinely for rapid sequence intubation in critically ill patients in North America.[1,43]

Goals of This Investigation

Our main objective was to synthesize the available evidence on the effect of a single bolus dose of etomidate on serum cortisol levels compared with other intravenous induction agents. Secondary objectives were to compare the effect of etomidate on mortality, number of days in the ICU, in hospital, and on ventilator.

MATERIALS AND METHODS

Study Design

This was a quantitative and qualitative systematic review of the literature. Ethics approval was not required for this study because it did not involve the use of human subjects or medical records.

A professional librarian (M.M.D.W.) and study author (C.M.H.) developed a systematic search strategy that was adapted for and applied to each of the following electronic bibliographic reference databases: MEDLINE (1950 to June 2008), CINAHL (1982 to June 2008), EMBASE (1980 to June 2008), LILACS (1982 to June 2008), International Pharmaceutical Abstracts (1970 to June 2008), Web of Science (1980 to June 2008), Cochrane Central Register of Controlled Trials (CENTRAL, second quarter 2008), the Cochrane Database of Systematic Reviews (second quarter 2008), the Database of Abstracts of Reviews of Effects (DARE, second quarter 2008), and BIOSIS Previews (1969 to June 2008). The MEDLINE search combined Medical Subject Headings terms and key words for etomidate, imidazoles, benzyl compounds, endotracheal intubation, anesthesia, laryngoscopy, sedation, critical care, intensive care, emergency, adrenal insufficiency, and terms for relevant outcome measures (Appendix E1, available online at http://www.annemergmed.com). These terms were then translated into equivalent terms in the other databases. Scope notes for each term were reviewed and searches refined to incorporate previous indexing terms. Filters for randomized controlled trials, controlled clinical trials, and observational studies were applied. No language filters were used.

We hand searched the following medical journals from 1997 to 2008: *Annals of Emergency Medicine*, *Academic Emergency Medicine*, *Canadian Journal of Emergency Medicine*, *Emergency Medicine Clinics of North America*, *Journal of Emergency Medicine*, *Anesthesiology*, *Canadian Journal of Anesthesia*, *Anesthesia and Analgesia*, *British Journal of Anesthesia*, *Journal of Trauma*, *Intensive Care Medicine*, and *Critical Care Medicine*. Conference proceedings of major emergency medicine and anesthesia conferences were searched from 1997 to 2008 to identify data published in abstract form only. A gray literature search included electronic searches of the clinical trial registry Web sites Current Controlled Trials, National Health Service–The National Research Register, and ClinicalTrials.gov to identify ongoing trials.[44-46] Authors of all ongoing trials were contacted for unreported data. We also searched for gray literature with the search engine Google and relevant key words. Content experts were contacted, and Web sites of manufacturers of intravenous induction agents, and the professional societies of emergency medicine, anesthesia, and critical care were searched for abstracts, articles, and any unpublished data.

The bibliographies of all relevant retrieved articles identified in the search above were hand searched for any missed studies. During the course of the review, we found 4 additional articles that were published after completion of our formal searches by scanning the current literature.[41,47-49]

Studies were included if they reported human data comparing the effect of a bolus dose of etomidate with another rapidly acting intravenous induction agent currently used for rapid sequence intubation. Studies had to report on at least one relevant outcome measure and enroll patients older than 16 years. Studies that examined etomidate infusions, did not use a comparator induction agent, used etomidate for purposes other than endotracheal intubation, enrolled only pediatric patients or patients receiving exogenous steroids, or were written in languages other than English, French, and German were excluded.

Data Collection and Processing

Two study authors (C.H.K.-S. and T.C.Y.) screened all retrieved titles for potential eligibility, using the aforementioned criteria, and excluded studies that clearly did not meet inclusion criteria according to their title. Using the same criteria, the same authors then reviewed abstracts of all remaining titles. If eligibility was possible, the full-text article was retrieved and reviewed independently by 2 study authors (C.H.K.-S. and C.M.H.). After eligibility was determined, the same study authors abstracted data from all included English studies independently in duplicate, using standardized piloted data abstraction forms (Appendix E2, available online at http://www.annemergmed.com). Data on identifying information of the study, study design, study objectives, indication for intubation, experimental and control interventions, cointerventions, method of randomization, concealment of treatment allocation, blinding, loss to follow-up, statistical analysis, and outcomes of interest were abstracted. Any disagreements over a study's eligibility or data abstraction points were resolved by achieving consensus through discussion. Primary study authors were contacted for data clarification purposes when necessary. Whenever results of the comparison group reported aggregate data on patients intubated with and without drugs, we contacted study authors for patient-level data and included data on patients intubated with comparator drugs, if made available. Data on patients intubated without the use of an induction agent were excluded. One study author (C.M.H.) reviewed and abstracted data from all French and German

articles. The data abstractors were not blinded to authorship or journal.

Outcome Measures

The primary outcome measure was the pooled mean difference in serum cortisol levels in patients induced with etomidate compared with other induction agents. Secondary outcome measures were the odds of dying and the mean difference in the number of days in ICU, receiving ventilator support, and in hospital for patients induced with etomidate compared with control.

Two authors (C.H.K.-S. and C.M.H.) independently assigned a Jadad score to all randomized controlled trials (Appendix E2, available online at http://www.annemergmed.com).[50] Trials with Jadad scores of 1 to 3 were rated as low quality; those with scores of 4 and 5, high quality. Because no universal scale is available for measuring the quality of nonrandomized studies, we followed the recommendations of the Meta-analysis of Observational Studies in Epidemiology guidelines and rated the likelihood of selection, performance, attrition, and detection bias for these studies (Appendix E2, available online at http://www.annemergmed.com).[51] Any disagreements over the scores were discussed and resolved by consensus.

Primary Data Analysis

We decided a priori to limit pooling of data to outcomes reported by a minimum of 4 studies of the same design conducted in comparable patient populations that reported the same outcome measures. Random-effects meta-analysis was carried out for each pooled comparison between treatment and control at a single point. To pool data on changes from baseline at successive points, differences from baseline were combined meta-analytically, assuming a conservative correlation over time of 0.5 in the calculations of the corresponding standard errors.[52] Statistical heterogeneity was assessed with the Cochran Q test, with a *P*-value cutoff of $P<.1$ considered significant. Ninety-five percent confidence intervals (CIs) were calculated to qualify the pooled point estimates. We tested the significance of the pooled mean differences with the z test and considered $P<.05$ significant. Stata software (version 9.1; StataCorp, College Station, TX) was used in the analysis.

Sensitivity Analysis

Because previous literature indicated a dose-response relationship between the degree of adrenal suppression and etomidate dose, we removed studies that used lower than usual (<0.3 mg/kg) and greater than usual (>0.35 mg/kg) etomidate doses.[53] We did not use JADAD scores in our sensitivity analysis, because only one study reviewed that met our criteria for pooling was rated with a high-quality score.

RESULTS

We identified 3,083 titles, of which 2,763 were excluded on title review and 195 on abstract review. We retrieved and reviewed the full texts of 125 articles (Figure 1). We included 18 randomized controlled trials,[4,27-35,47,49,53-58] 1 nonrandomized prospective study,[48] and 1 retrospective study.[59] We included data from 1 recent randomized controlled trial in which data on patients intubated with and without drugs were reported in aggregate, but for which study authors provided access to primary data.[48] In addition, we included 1 randomized controlled trial published online as a corrected proof during the writing of this article.[49] Tables 1 and 2 characterize the included studies.

All included studies used etomidate in doses of 0.2 mg/kg to 0.4 mg/kg, with the majority using doses of 0.3 mg/kg. Standard intubating doses of thiopental, propofol, ketamine, and benzodiazepines with or without narcotics were used as comparator induction agents. Very low doses of midazolam were used in several studies.[4,30,47,58]

Main Results

Sixteen randomized controlled trials investigated the relationship between etomidate and comparator induction agents with regard to cortisol levels, reporting data on 810 patients.[27-35,47,49,53-57] Twelve randomized controlled trials were clinically homogenous and enrolled elective surgical patients of American Society for Anesthesiologists (ASA) grades 1 or 2,[27-35,53,56,57] and 4 were conducted with critically ill patients.[47,49,54,55]

Fourteen of 16 randomized controlled trials reported significant decreases in serum cortisol level postinduction with etomidate. We pooled data from 9 studies that appeared to be clinically homogenous and enrolled ASA grade 1 and 2 elective surgical patients (n=201 patients) and that reported cortisol levels at the same intervals postinduction (Figure 2).[28,29,31-34,53,56,57] There were statistically significant differences between the control and etomidate groups at 1 hour (difference 6.1 μg/dL; 95% CI 2.4 to 9.9 μg/dL; $P=.001$), 2 hours (difference 13.3 μg/dL; 95% CI 7.7 to 18.9 μg/dL; $P<.001$), 3 hours (difference 12.6 μg/dL; 95% CI 6.6 to 18.4 μg/dL; $P<.001$), and 4 hours (difference 16.4 μg/dL; 95% CI 9.7 to 23.1 μg/dL; $P<.001$) postinduction. There were no statistically significant differences after 5 hours (difference 8.7 μg/dL; 95% CI –2.6 to 19.9 μg/dL; $P=.13$). Because statistical heterogeneity was high in our pooled estimates (Cochrane Q, $P<.1$ for all estimates) and previous reports reported a dose-response relationship between etomidate and the degree of adrenal suppression observed, we removed trials with lower (<0.3 mg/kg)[31,53] and higher than standard doses of etomidate (>0.35 μg/dL).[33,56,57] This reduced statistical heterogeneity while yielding no significant changes in our estimates. We did not attempt to remove low-quality studies, because only one study included in our meta-analysis of cortisol levels was rated with a high-quality Jadad score.[53]

Data from the 3 randomized controlled trials enrolling elective surgical patients that we could not pool were consistent with these pooled results.[27,30,35] Two reported statistically significant suppression of cortisol levels between 4 and 6 hours postinduction in etomidate-treated patients.[27,30] The third reported no difference in cortisol levels within minutes of

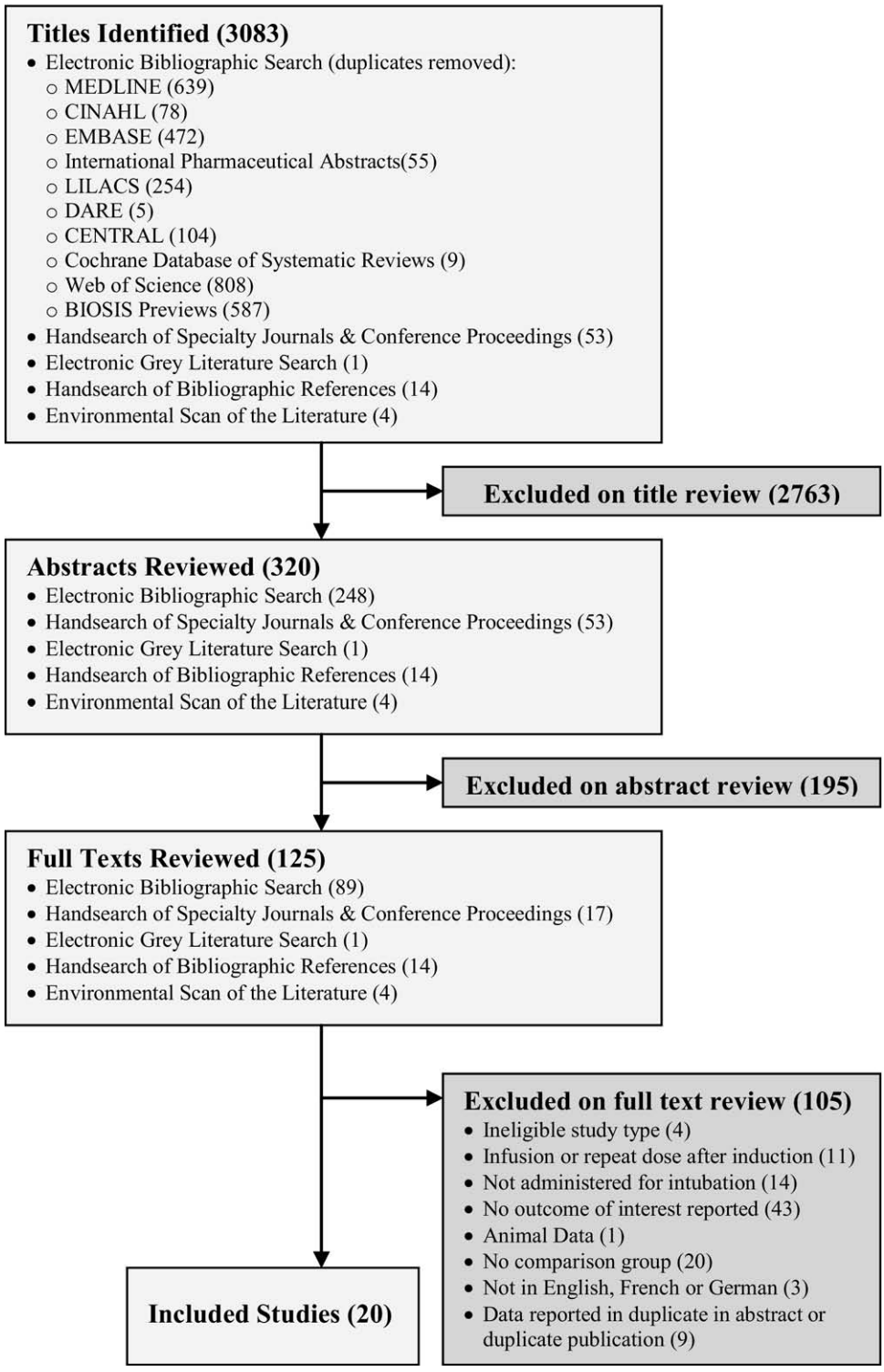

Figure 1. QUOROM flow diagram for selection of trials.

induction and immediately postoperatively and is therefore in keeping with other studies that report a delay in the onset of adrenal suppression.[35]

Four randomized controlled trials enrolling ASA grade I and II surgical patients reported cortisol levels between 7 and 12 hours postinduction.[33,34,55,56] All studies reported cortisol values at or above baseline during this interval.

Four randomized controlled trials enrolled critically ill patients. We were unable to pool their data because the trials reported cortisol levels at different times postinduction.[47,49,54,55] The largest and

Table 1. Characteristics of included randomized controlled trials.

Study	N	Setting	Patients	Comparator	Relevant Outcomes	Authors' Conclusions	JADAD Score
Absalom, 1999[54]	35	ICU	Urgent GA, ASA >3	Thiopental	1. Cortisol levels 2. Mortality	1. No difference at 24 h 2. No difference	2
Allolio, 1984[28]	29	OR	Elective GA	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 2–4 h postinduction	1
Allolio, 1985[27]	14	OR	Elective GA	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 3.5 h postinduction	1
Allolio, 1984[29]	16	OR	Elective GA	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 1–4 h postinduction	1
Bendel, 2007[53]	66	OR	Elective GA	Propofol	1. Cortisol levels 2. Mortality 3. ICU LOS 4. Hospital LOS	1. Depressed cortisol levels in etomidate group postoperatively 2. No difference 3. No difference 4. No difference	4
Börner, 1985[30]*	30	OR	Elective GA, ASA 1 and 2	Methohexital Midazolam†	Cortisol levels	Depressed cortisol levels in etomidate group postoperatively	1
Cooper, 1988[55]	11	OR	Urgent GA, ASA 3 and 4	Diazepam	Cortisol levels	No difference immediately postinduction, at 1 h, and at 12 h postinduction.	1
De Coster, 1985[31]	19	OR	Elective GA, ASA 1 and 2	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 1.5–6 h postinduction	1
Fellows, 1985[32]	10	OR	Elective GA, ASA 1 and 2	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 1.5–2 h	1
Fragen, 1984[33]	10	OR	Elective GA, ASA 1 and 2	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 30 min to 5 h postinduction	2
Hildreth, 2008[47]	30	Out-of-hospital, ED, ICU, OR	Critically ill, trauma	Midazolam‡	1. Cortisol levels 2. Mortality 3. LOS ICU 4. LOS ventilator 5. LOS hospital	1. Depressed cortisol levels in etomidate group 4–6 h postinduction 2. No difference 3. Longer LOS in etomidate group 8.1 vs 3.0 days 4. Longer LOS in etomidate group 6.3 vs 1.5 days 5. Longer LOS in etomidate group 13.9 vs 6.4 days	2
Jabre, 2009[49]	469§	Out-of-hospital, ED, ICU	Critically ill	Ketamine	1. Cortisol 2. Mortality 3. LOS ICU 4. LOS ventilator	Depressed cortisol levels in etomidate group 7h postinduction‖ No difference No difference No difference	3
Jacoby, 2006[4]	110	Out-of-hospital	Critically ill	Midazolam‡	Mortality	No difference	5
Montalban, 2001[56]	22	OR	Elective GA, obese	Thiopental	Cortisol levels	Depressed cortisol levels in etomidate group 2–6 h postinduction	1
Saranteas, 2004[57]	20	OR	Elective GA, obese	Propofol	Cortisol levels	Depressed cortisol levels in etomidate group 1–4 h postinduction	1
Schenarts, 2001[58]	31	ED	Critically ill	Midazolam†	1. Mortality 2. LOS ICU 3. LOS ventilator 4. LOS hospital	1. No difference 2. No difference 3. No difference 4. No difference	3
Sear, 1988[34]	9	OR	Elective GA, ASA 1 and 2	Thiopental	Cortisol levels	Depressed cortisol levels at the end of surgery and 4 h postinduction	1
Sebel, 1983[35]	20	OR	Elective GA	Thiopental	Cortisol levels	No difference 3 min postinduction and immediately postoperatively	1

GA, General anesthesia; *OR,* operating room; *LOS,* length of stay.
Unless otherwise noted, the following drug doses were used: etomidate 0.3 mg/kg intravenously, thiopental 3 to 6 mg/kg intravenously, propofol 2 to 3 mg/kg intravenously, midazolam 0.3 mg/kg intravenously, and methohexital 1.0 to 2.0 mg/kg intravenously.
*Etomidate 0.2 mg/kg intravenously.
†Midazolam 0.05 to 0.15 mg/kg intravenously.
‡Midazolam 7 mg intravenously.
§Six hundred fifty-five patients were randomized, 469 patients were analyzed in a modified intention-to-treat analysis, and 232 had cortisol levels tested.
‖(P. Jabre, personal communication, October 10, 2009).

Table 2. Characteristics of included nonrandomized studies.

Study	N	Setting	Patients	Comparator	Outcomes of Interest Reported	Authors' Conclusions	Risk of Bias			
							Selection	Performance	Attrition	Detection
Prospective observational studies										
Tekwani, 2009[48]	106	ED	Septic shock	Midazolam, other	1. Mortality 2. Hospital LOS	1. No difference 2. No difference	High	High	Moderate	Low
Retrospective studies										
Ray, 2007[59]	159	ICU or OR	Septic shock	Propofol, thiopental, other*	Mortality	No difference	High	Moderate	Moderate	Low

All outcomes for which no statistically significant differences were reported are recorded as "no difference." The drug doses used were as follows: etomidate 0.3 mg/kg intravenously, thiopental 3 to 5 mg/kg intravenously, propofol 2 to 2.5 mg/kg intravenously, and midazolam 0.3 mg/kg intravenously.
*Substudy of the CORTICUS trial.[21] Patients were randomized to low-dose hydrocortisone or placebo, and not with regard to etomidate use. Combined group of patients receiving midazolam, ketamine, fentanyl alone, or inhalational anesthesia.

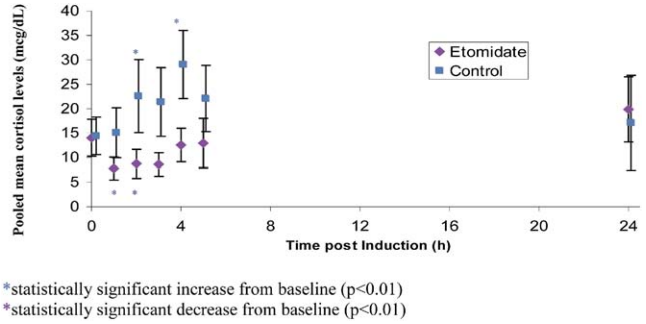

Figure 2. Pooled mean cortisol levels and 95% CIs over time in patients induced with etomidate compared with other agents. Z-tests were used to compare the 1, 2 and 4h pooled mean cortisol values within each group to the baseline values.

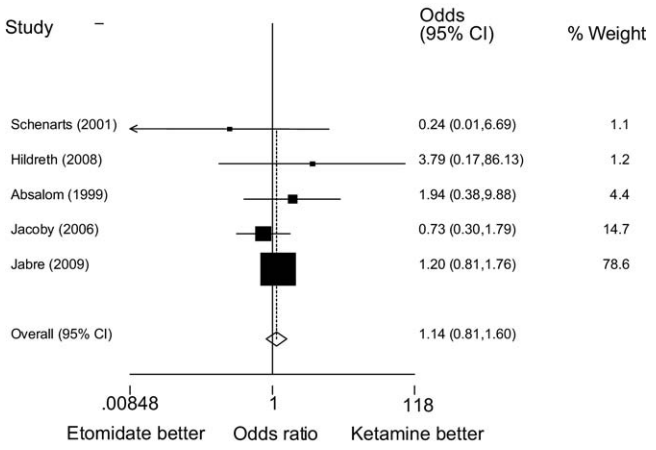

Figure 3. Individual and pooled OR estimates of mortality for patients treated with etomidate compared with control.

most robust of these randomized controlled trials enrolled 655 critically ill patients and reported cortisol levels for 232 patients.[49] Median cortisol levels were significantly depressed in patients induced with etomidate compared with ketamine (16.0 versus 25.0 μg/dL; $P<.0001$) at a median of 7h postinduction (P. Jabre, personal communication, October 10, 2009). Another randomized controlled trial enrolling intubated trauma patients reported significantly depressed cortisol levels 4 to 6 hours postinduction, consistent with data from elective surgical patients.[47] Two randomized controlled trials reported data at 24 hours, with the objective of determining whether adrenal suppression persists in critically ill patients, and found no difference.[54,55]

Six randomized controlled trials,[4,47,49,53,54,58] 1 prospective observational study,[48] and 1 retrospective study[59] reported data on mortality. Seven of 8 studies were conducted with critically ill patients.[4,47-49,54,58,59] None of the individual studies showed a statistically significant effect on mortality, but 5 studies, including the largest and most robust trial to date, showed point estimates indicating possible harm with etomidate. Data from 5 of the randomized controlled trials with critically ill patients (n=741) were pooled. The pooled odds ratio (OR) for mortality was 1.14 (95% CI 0.81 to 1.60; Q=2.83; P=.59) for patients treated with etomidate compared with control (Figure 3).

We were unable to pool the results of 2 studies because they were not randomized.[48,59] In a prospective study, Tekwani et al[48] compared the unadjusted mortality between 74 septic patients induced with etomidate and 32 patients induced with comparator agents and found no statistically significant difference in mortality. Ray and McKeown[59] reviewed data on 159 septic patients, of whom 74 received an induction agent, and also found no statistically significant difference between patient groups.

Four randomized controlled trials reported data on ICU[47,49,53,58] and 3 on ventilator length of stay.[47,49,58] Three of the studies were conducted with critically ill patients[47,49,58] and 1 in elective surgical patients.[53] The only study that reported a significant difference in both outcomes enrolled 60 trauma patients requiring ED rapid sequence intubation, of which only 30 were randomized and included in the analysis. The authors reported significantly longer ventilator length of stay (6.3 versus

1.5 days; $P=.007$) and ICU length of stay (8.1 versus 3.0 days; $P=.011$) in the etomidate group but also reported greater Injury Severity Scores at baseline in the etomidate-treated patients.[47]

Three randomized controlled trials[47,53,58] and 1 controlled prospective observational study[48] reported data on hospital length of stay. Only 1 presented adjusted analyses to account for potential confounders.[48] One randomized controlled trial reporting data on 66 patients undergoing elective surgery found no difference in hospital length of stay.[53] The other 3 studies were conducted with critically ill trauma,[47] septic,[48] and ED patients requiring rapid sequence intubation.[58] Of these studies, 2 reported no difference in hospital length of stay,[48,58] and 1 found that patients exposed to etomidate had a longer hospital length of stay (13.9 versus 6.4 days; $P=.007$).[47]

LIMITATIONS

This quantitative and qualitative systematic review of the literature was limited in several ways. As in all systematic reviews, our synthesis of the data was limited by the quality of evidence presented in the primary studies. Many randomized controlled trials conducted to date on this topic enrolled small numbers of patients and were of poor quality in terms of reporting, blinding, and treatment allocation. Despite these limitations, the data derived were remarkably consistent with regard to cortisol levels and pointed to transient adrenal suppression starting at around 1 hour postinduction with etomidate, suggesting that this finding is robust.

Most included studies were conducted with elective surgical patients, and only 8 studies meeting our inclusion criteria were conducted in critically ill patients, the patient population most relevant to emergency physicians. Although we found the data on adrenal suppression from critically ill patients to be consistent with data from elective surgical patients, the data on prolonged adrenal suppression (from 12 to 48 hours postinduction) in critically ill patients were limited, and therefore a more prolonged effect in this patient population cannot be excluded. In addition, the patient populations and methodologies used in studies on critically ill patients were more diverse than for elective surgical patients, precluding our ability to pool these data.

Third, although our search strategy was exhaustive, selection, retrieval, and publication bias are always a concern in systematic reviews. To minimize these types of biases, a professional librarian assisted in all searches and adapted searches to multiple electronic databases. Despite substantial efforts to find all potentially relevant data, we would still have been less likely to find negative-result studies because they are less likely to be published. In addition, we were unable to include studies published in languages other than English, French, and German and were unable to abstract data in duplicate from non-English studies. In addition, many studies reported data in graphic rather than numeric format. Because of this, we were unable to report measures of interrater agreement on the data retrieval process. This would have required defining ranges of agreement for data abstracted from graphic format, which would have been different than agreement criteria for data abstracted from numeric format.

Fourth, the secondary outcomes we studied included ICU, ventilator, and hospital length of stay. Local practice patterns, resource availability, staffing levels, and time of day can influence any of these outcomes. In addition, none of the studies reviewed were powered to detect a difference in any of these endpoints, making it difficult to draw conclusions on these outcomes.

Finally, the etomidate dosing range represented in this review is a reflection of the dosing ranges used in the primary studies. Because previous studies indicated a dose-response relationship between etomidate and the degree of adrenal suppression,[53] it is possible that our study underestimates the severity or duration of adrenal suppression associated with higher doses of etomidate.

DISCUSSION

Our quantitative and qualitative systematic review found consistent evidence that cortisol levels are suppressed by a single bolus of etomidate between 1 and 4 hours postinduction. Only a few studies, most of which were conducted with elective surgical patients, examined cortisol levels between 6 and 24 hours postinduction and most were consistent with recovery of the adrenocortical axis by 8 hours.

This latter finding contrasts with observational data derived from 2 large randomized controlled trials on corticosteroid replacement in septic shock that indicate that etomidate-associated adrenal suppression is apparent 12 hours,[12,20] 24 hours,[18,21] and even up to 72 hours[10] after induction with etomidate. These differences may be explained by differences in the patient populations studied, in the etomidate doses used, and in study methodology. The observational data from the study by Annane et al[20] and the Corticosteroid Therapy of Septic Shock Study Group (CORTICUS)[21] trial were derived from critically ill patients whose overall 28-day mortality rates were 58% and 33%, respectively, clearly sicker patients than those enrolled in trials meeting inclusion criteria for our review and meeting criteria for pooling.

Our pooled point estimate of the effect on mortality was consistent with a 14% increase in the odds of death with etomidate, but this effect was not statistically significant. None of the individual studies reviewed were powered to detect a mortality difference, nor were any designed as equivalence studies, making it difficult to draw conclusions from this finding. Using estimates from Jabre et al,[49] we calculated the hypothetical sample size required to detect a 10% relative (and 3% absolute) mortality difference with 80% power at a .05 significance level. More than 7,600 critically ill patients not meeting exclusion criteria after intubation would have to be enrolled to detect a significant mortality difference, a daunting task and likely why Jabre et al[49] used a surrogate marker, the Sequential Organ Failure Assessment Score, as primary endpoint and combined subgroups of patients to reduce sample size requirements.[49]

Because observational data have indicated the potential for harm with etomidate,[12,18,21,41,42] we believe that the burden of proof is to show that etomidate is *as safe as* other induction agents. By convention, in order to prove safety, ie, that etomidate is *not inferior* to other induction agents, a study designed with a noninferiority hypothesis

demonstrating lack of overlap of the 95% CIs of the treatment effect to a cutoff indicating harm would be required.[60] Neither the trial by Jabre et al[49] nor our review met this methodological standard. For this reason, neither the trial by Jabre et al[49] nor our review can be considered sufficient evidence to prove the safety of etomidate.

The wide CIs of the point estimate for mortality that we obtained reflect the remaining uncertainty in our pooled estimate for mortality. They are consistent with the odds of dying after induction with etomidate being 19% lower to 60% higher than with control agents. Therefore, although our findings are concerning, they are also consistent with equivalence or even superiority of etomidate.

Further complicating the interpretation of our findings is that few high-quality studies have compared the safety profiles of other induction agents. None of the induction agents used in the ED are devoid of potential adverse effects. Our study did not examine immediate adverse events such as hemodynamic and cardiodepressant adverse effects and factors such as ease of tracheal intubation and simplicity of use that also need to be taken into consideration when choosing the most appropriate induction agent for a given patient.

The available evidence suggests that etomidate suppresses adrenal function transiently, without demonstrating a significant effect on mortality. However, to our knowledge no studies to date have been powered to detect a difference in mortality or time in the hospital, the ICU, or receiving ventilator support. According to robust evidence that etomidate transiently decreases adrenal function and that a significant effect on mortality cannot be excluded, alternate induction agents may be considered for use in rapid sequence intubation, particularly for septic patients. More data are needed to determine etomidate's effect on mortality.

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APPENDIX E1.

Medline Search Strategy

1 Imidazoles/ (30754)
2 limit 1 to yr="1969 - 1985" (7608)
3 Benzyl Compounds/ (3022)
4 limit 3 to yr="1969 - 1975" (1689)
5 hypnomidate.mp. (29)
6 Amidate.mp. (85)
7 Etomidate/ (1319)
8 Etomidat$ Lipuro.mp. (6)
9 Et?omidate.mp. (1782)
10 R 26 490.mp. (1)
11 r-26490.mp. (3)
12 R 16659.mp. (1)
13 radenar#on.mp. (10)
14 or/2,4-13 (10636)
15 Intubation, Intratracheal/ (23136)
16 Intubation/ (4139)
17 intubat$.mp. (49481)
18 (intra?tracheal adj5 intub$).mp. (23197)
19 anesthesia/ (35368)
20 anesthesia, intravenous/ (9182)
21 an?esthesia.mp. (183044)
22 anesthesia, general/ (28328)
23 anesthetics/ (13840)
24 an?esthetic$.mp. (83611)
25 (airway adj5 protection).mp. (404)
26 Laryngoscopy/ (6841)
27 laryngoscop$.mp. (9836)
28 (sedative or sedate or sedation).mp. (25932)
29 "Hypnotics and Sedatives"/ (17133)
30 Deep Sedation/ (31)
31 single bolus dose.mp. (243)
32 induction.mp. (315418)
33 Conscious Sedation/ (4626)
34 limit 33 to yr="1991 - 2007" (4429)
35 or/15-32,34 (589597)
36 14 and 35 (1780)
37 intensive care units/ or burn units/ or coronary care units/ or recovery room/ or respiratory care units/ (28901)
38 Intensive Care/ (9844)
39 Critical Care/ (19598)
40 Emergencies/ (30070)
41 emergenc$.mp. (176957)
42 Emergency Treatment/ (5660)
43 air ambulances/ (1160)
44 ambulance$.mp. (7345)
45 emergency service, hospital/ or trauma centers/ (31599)
46 Emergency medical services/ (22778)
47 trauma.mp. (125768)
48 Critical Illness/ (8832)
49 ((intensive or critical$ or serious$) adj5 (ill$ or care or sick)).mp. (109078)
50 ICU.mp. (15216)
51 or/37-50 (393538)
52 14 and 51 (227)
53 Mortality/ (29010)
54 mortality.mp. (306931)
55 heart arrest/ (17300)
56 "Length of Stay"/ (39578)
57 Respiration, Artificial/ (29744)
58 Ventilators, Mechanical/ (7056)
59 ventilator$.mp. (35253)
60 Postoperative Care/ (44936)
61 Intraoperative Care/ (10929)
62 Perioperative Care/ (3982)
63 treatment outcome/ (341575)
64 clinical outcome.mp. (25482)
65 "outcome and process assessment (health care)"/ or "outcome assessment (health care)"/ or "process assessment (health care)"/ (49399)
66 risk factors/ (357017)
67 risk$.mp. (958610)
68 Survival Analysis/ (68268)
69 (adverse adj3 effect$).mp. (71707)
70 fatal outcome/ (34541)
71 Adrenal Insufficiency/ (3570)
72 (adrenocortical adj4 (suppression or function)).mp. (1880)
73 Blood Pressure/ (203109)
74 blood pressure.mp. (286656)
75 exp hemodynamics/ (483502)
76 hemodynamic$.mp. (153262)
77 hypotension/ (15106)
78 hypotension.mp. (43236)
79 or/53-78 (2201296)
80 14 and 79 (1521)
81 ae.fs. (1026759)
82 ct.fs. (12876)
83 mo.fs. (294644)
84 de.fs. (1907951)
85 co.fs. (1264586)
86 or/81-85 (4105434)
87 14 and 86 (5278)
88 or/36,52,80,87 (5881)
89 Random allocation/ (61799)
90 Double blind method/ (98709)
91 Single blind method/ (12253)
92 clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or controlled clinical trial/ or multicenter study/ or randomized controlled trial/ (552009)
93 or/89-92 (600360)
94 (clinic$ adj25 trial$).tw. (147520)
95 Placebos/ (27469)
96 cross-over studies/ (22319)

97 (crossover or cross-over or cross over).tw. (41176)
98 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (98179)
99 placebo$.tw. (111544)
100 randomly allocated.tw. (10346)
101 (allocated adj2 random).tw. (628)
102 or/94-101 (318403)
103 or/93,102 (738414)
104 Case report.tw. (135325)
105 Letter.pt. (631379)
106 Historical article.pt. (251747)
107 or/104-106 (1010448)
108 103 not 107 (724553)
109 Epidemiologic studies/ (4122)
110 exp case control studies/ (397099)
111 exp cohort studies/ (681903)
112 Case control.tw. (42104)
113 (cohort adj (study or studies)).tw. (36283)
114 Cohort analy$.tw. (1817)
115 (Follow up adj (study or studies)).tw. (28047)
116 (observational adj (study or studies)).tw. (17068)
117 Longitudinal.tw. (80853)
118 Retrospective.tw. (149608)
119 Cross sectional.tw. (793810
120 Cross-sectional studies/ (90190)
121 or/109-120 (1190781)
122 or/108,121 (1745351)
123 animal/ not (animal/ and human/) (3226402)
124 122 not 123 (1668717)
125 88 and 124 (819)
126 limit 125 to yr="1970 - 2008" (809)

APPENDIX E2.

DATA EXTRACTION FORM

Study Information	**Authors:**	**Year:**

METHODS

Study Design	❒ Randomized Controlled Trial ❒ Non-randomized Controlled Trial ❒ Prospective Observational Controlled Study/Cohort Study ❒ Retrospective Comparison Study/Chart Review with Comparison Group ❒ Case Control Study ❒ Historical Control Study	
Objectives 1° **2°**		
Study Eligibility for Systematic Review:	**Inclusion (Tick all)** ❒ Comparative Study ❒ Bolus of Etomidate ❒ Comparison: Prop/Thio/Methohex/Ket/BDZ ❒ Adult patients ❒ Endotracheal Intubation ❒ Report at least one outcome of measure	**Exclusion (None can be ticked)** ❒ Ineligible Study Type ❒ Pediatric data only ❒ Etomidate Infusion ❒ Etomidate for Procedural sedation ❒ All patients on exogenous steroids prior induction ❒ Etomidate for ECT/Sz induct'n ❒ Language other that E/F/G
Participants: (Study's incl/excl criteria)	**Inclusion:**	**Exclusion:**
Study's indication for intubation		
Criteria to determine need for Intubation:		
Exp Intervent (dose, route)		
Control Intervent (dose, route)		
Co-Interventions (steroids, pressors)		
Setting/Region		
Study Duration		

OUTCOME MEASURES AND DEFINITIONS

***A priori* defined outcome measurements of the study & how measured?**	
Intubation Success	
ACTH stim test	
Cortisol levels	
Were supplemental steroids used/reported?	
BP, HR (cutoffs, values, times measured)	
LOS ventilator	
LOS ICU	
Deaths	

Further Notes for Results:

Results:	
Analysis: Intention to Treat? Appropriate Stats? Other comments?	
Other:	

JADAD SCORE FOR RCTS ONLY:

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated)?	
Was the study described as double blind?	
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	
Was there a description of withdrawals and dropouts?	
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	

JADAD SCORE: Either give a score of 1 point for each"yes" or 0 points for each "no." **JADAD SCORE**:

Citation: