CHEST™

Single-Dose Etomidate Does Not Increase Mortality in Patients With Sepsis

A Systematic Review and Meta-analysis of Randomized Controlled Trials and Observational Studies

Wan-Jie Gu, MSc; Fei Wang, MD; Lu Tang, MD; and Jing-Chen Liu, MD

BACKGROUND: The effect of single-dose etomidate on mortality in patients with sepsis remains controversial. We systematically reviewed the literature to investigate whether a single dose of etomidate for rapid sequence intubation increased mortality in patients with sepsis.

METHODS: PubMed, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) were searched for randomized controlled trials (RCTs) and observational studies regarding the effect of single-dose etomidate on mortality in adults with sepsis. The primary outcome was all-cause mortality. The Mantel-Haenszel method with random-effects modeling was used to calculate pooled relative risks (RRs) and 95% CIs.

RESULTS: Eighteen studies (two RCTs and 16 observational studies) in 5,552 patients were included. Pooled analysis suggested that single-dose etomidate was not associated with increased mortality in patients with sepsis in both the RCTs (RR, 1.20; 95% CI, 0.84-1.72; $P = .31$; $I^2 = 0\%$) and the observational studies (RR, 1.05; 95% CI, 0.97-1.13; $P = .23$; $I^2 = 25\%$). When only adjusted RRs were pooled in five observational studies, RR for mortality was 1.05 (95% CI, 0.79-1.39; $P = .748$; $I^2 = 71.3\%$). These findings also were consistent across all subgroup analyses for observational studies. Single-dose etomidate increased the risk of adrenal insufficiency in patients with sepsis (eight studies; RR, 1.42; 95% CI, 1.22-1.64; $P < .00001$).

CONCLUSIONS: Current evidence indicates that single-dose etomidate does not increase mortality in patients with sepsis. However, this finding largely relies on data from observational studies and is potentially subject to selection bias; hence, high-quality and adequately powered RCTs are warranted.

CHEST 2015; 147(2):335-346

Manuscript received April 25, 2014; revision accepted September 3, 2014; originally published Online First September 25, 2014.

ABBREVIATIONS: MV = mechanical ventilation; RCT = randomized controlled trial; RR = relative risk

AFFILIATIONS: From the Department of Anaesthesiology (Mr Gu and Dr Liu), First Affiliated Hospital of Guangxi Medical University, Nanning; and Department of Anaesthesiology (Drs Wang and Tang), General Hospital of Jinan Military Command, Jinan, China.

FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

CORRESPONDENCE TO: Jing-Chen Liu, MD, Department of Anaesthesiology, First Affiliated Hospital of Guangxi Medical University, 22 Shuangyong Rd, Nanning 530021, China; e-mail: jingchenliu1964@sina.cn

DOI: 10.1378/chest.14-1012

In patients with sepsis, endotracheal intubation is a common and important procedure to secure the airway and guarantee sufficient ventilation. However, it can lead to life-threatening complications because of the vulnerable hemodynamic status of patients with sepsis.[1] To avoid such complications, rapid sequence intubation with administration of an induction agent frequently is required. Etomidate often is used as an induction drug for rapid sequence intubation because it allows for a rapid, smooth, and hemodynamically stable procedure.[2] However, etomidate inhibits adrenal mitochondrial 11-β-hydroxylase activity and can cause reversible adrenal insufficiency,[3,4] which may restrict its use in patients with sepsis who are prone to relative adrenal insufficiency.[5] Although there is no controversy about etomidate causing adrenal insufficiency, the effect of etomidate on mortality in sepsis remains an issue.[6] So far, studies reporting the effect of etomidate on mortality in sepsis have conveyed conflicting results. Furthermore, due to small sample sizes, these studies were not adequately powered to detect the effect of etomidate on mortality in patients with sepsis. Thus, to provide the latest and most convincing evidence, we systematically reviewed the current available literature to investigate whether single-dose etomidate increases mortality in patients with sepsis. The secondary objective was to evaluate the effect of single-dose etomidate on adrenal insufficiency, length of hospital and ICU stay, and duration of mechanical ventilation (MV).

Materials and Methods

Literature Search and Selection Criteria

This systematic review and meta-analysis was conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[7] PubMed, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials) were searched for records reporting the effect of single-dose etomidate on mortality in patients with sepsis. The search strategy is shown in Table 1. No language restriction was imposed. The last search was run on July 16, 2014. Two independent investigators carried out the initial search, deleted duplicate records, screened the titles and abstracts for relevance, and identified each as excluded or requiring further assessment. We reviewed the full-text articles designated for inclusion and manually checked the references of the retrieved articles and previous reviews to identify additional eligible studies.

Studies meeting the following criteria were included: (1) population: adult patients with sepsis, severe sepsis, or septic shock; (2) intervention: single-dose etomidate; (3) comparison: other sedatives or no agent; (4) outcome: mortality (either hospital or 28-day); and (5) design: randomized controlled trials (RCTs) and observational studies (prospective or retrospective cohort studies). Agreement regarding study inclusion was assessed using the Cohen κ statistic.[8]

Data Extraction and Quality Assessment

Data extraction was performed by L. T. and confirmed independently by F. W. The following information was extracted from each study: first author, year of publication, country, study design, patient characteristics, number of patients enrolled, intervention, and outcome data (mortality, adrenal insufficiency, length of hospital stay, length of ICU stay, and duration of MV). When the same patients were reported in several publications, we retained only the largest study to avoid duplication of information. Extracted data were entered into a standardized Excel (Microsoft Corporation) file. Discrepancies were resolved by discussion between the two investigators. The primary outcome was all-cause mortality. Secondary outcomes were adrenal insufficiency, length of hospital and ICU stay, and duration of MV. The Cochrane risk of bias tool was adopted to assess the risk of bias for each RCT.[9] Observational studies were evaluated using the Newcastle-Ottawa Scale.[10]

Statistical Analysis

Data were analyzed separately for RCTs and observational studies. Differences were expressed as relative risk (RR) with 95% CI. Heterogeneity across studies was tested with the I^2 statistic, which is a quantitative measure of inconsistency across studies. Studies with an I^2 statistic of 25% to 50% were considered to have low heterogeneity, those with an I^2 statistic of 50% to 75% were considered to have moderate heterogeneity, and those with an I^2 statistic of $>75\%$ were considered to have high heterogeneity. $I^2 > 50\%$ indicates significant heterogeneity.[11] The Mantel-Haenszel method with random-effects modeling was used to calculate pooled RRs and 95% CIs.

Post hoc analysis of RCTs was considered equivalent to observational studies. In addition, subgroup analyses for observational studies were conducted according to study design (post hoc analysis of RCTs vs cohort studies), population (sepsis vs severe sepsis or septic shock), setting (single center vs multicenter), mortality end point (28-day vs hospital), sample size (≥ 500 vs < 500), and region (North America vs Europe vs Asia). The subgroup analyses were performed only for mortality due to small numbers of studies for other outcomes. We also investigated the influence of a single study on the overall pooled estimate by omitting one study in each turn for observational studies.

Publication bias was assessed by visually inspecting a funnel plot in which the log RRs were plotted against their SEs. The presence of publication bias was also evaluated by using the Begg and Egger tests.[12,13] $P < .05$ was considered statistically significant, except where otherwise specified. All statistical analyses were performed using Stata 12.0 (StataCorp LP) and RevMan 5.2 (Nordic Cochrane Centre).

Results

Study Identification and Selection

A total of 424 records were identified from the initial database search. Ninety-eight records were excluded for duplicates, and 306 records were excluded for various reasons based on the titles and abstracts (reviews, letters, animal studies, or irrelevant to the analysis). The remaining 20 full-text articles were assessed for eligibility, and two were excluded because they focused on children.[14,15] Finally, 18 studies were included in the meta-analysis.[16-33] The selection process is shown in Figure 1. The Cohen κ statistic for agreement on study inclusion was 0.91.