Etomidate as an induction agent for endotracheal intubation in critically ill patients: A meta-analysis of randomized trials

Yuki Kotani, MD, Gioia Piersanti, Giacomo Maiucci, Stefano Fresilli, MD, Stefano Turi, MD, Giada Montanaro, Alberto Zangrillo, MD, Todd C. Lee, MD, MPH, Giovanni Landoni, MD

Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy
School of Medicine, Vita-Salute San Raffaele University, Milan, Italy
Department of Intensive Care Medicine, Kameda Medical Center, Kamogawa, Japan
Division of Infectious Diseases, Department of Medicine, McGill University, Montreal, Quebec, Canada

ARTICLE INFO

Keywords:
Systematic review
Meta-analysis
Etomidate
Intubation
Intensive care
Mortality

ABSTRACT

Purpose: We performed a meta-analysis of randomized controlled trials to evaluate if etomidate impacted mortality in critically ill adults when compared with other induction agents.

Materials and methods: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for randomized controlled trials which compared etomidate with any other induction agent in critically ill adult patients undergoing endotracheal intubation. The primary outcome was mortality at the main timepoint defined by the study. We conducted a fixed-effects meta-analysis for the risk ratio. Using that risk ratio and 95% confidence interval, we then estimated the probability of any harm (RR > 1) and the number needed to harm ≤ 100 (RR ≥ 1.05).

Results: We included 11 randomized trials comprising 2704 patients. We found that etomidate increased mortality (319/1359 [23%] vs. 267/1345 [20%]; risk ratio (RR) = 1.16; 95% confidence interval (CI), 1.01–1.33; P = 0.03; I² = 0%; number needed to harm = 31). The probabilities of any increase and a 1% increase (NNH ≤ 100) in mortality were 98.1% and 92.1%, respectively.

Conclusions: This meta-analysis found a high probability that etomidate increases mortality when used as an induction agent in critically ill patients with a number needed to harm of 31.

1. Background

Endotracheal intubation is a common intervention in intensive care unit (ICU) settings [1]. Hemodynamic instability often occurs during or after intubation and is associated with mortality. Anesthetic agents given at the time of endotracheal intubation may contribute to this risk because they can cause or worsen cardiovascular collapse [2,3]. Etomidate is recommended in clinical guidelines as an induction agent for endotracheal intubation in critically ill patients [4,5] because of both its rapid onset and neutral effect on hemodynamic stability [6].

However, etomidate suppresses cortisol production through the inhibition of 11-beta-hydroxylase in a dose-dependent manner, which may increase the risk of subsequent organ dysfunction or death [7,8]. One meta-analysis showed a statistically significant increased risk of mortality in patients receiving etomidate [9], while other meta-analyses found no significant differences [10,11]. A meta-analysis of randomized controlled trials (RCTs) found that etomidate was not associated with a statistically significant increase in mortality (odds ratio (OR), 1.15; 95% confidence interval (CI), 0.86–1.53), but increased adrenal insufficiency and multiorgan dysfunction in critically ill patients [12]. Subsequently, a large randomized controlled trial found that etomidate was associated with higher mortality than ketamine in critically ill patients requiring emergency intubation [13].

Considering the controversy in the prior meta-analyses [9-12] and...
the presence of at least one new RCT showing increased mortality [13], we conducted an updated systematic review and meta-analysis to test the hypothesis that etomidate would increase mortality in critically ill patients requiring endotracheal intubation compared with any other anesthetic agent.

2. Methods

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] and registered the review protocol in the PROSPERO International prospective register of systematic reviews, registration number CRD42022355667 on September 13, 2022. Our review question was built using the PICO (Population, Intervention, Comparison, Outcome, Study design) framework: among adult critically ill patients (P); does etomidate (I); compared with any comparator (C); increase mortality at the main timepoint defined by trial authors (O); in randomized controlled trials (S)?

2.1. Search strategy and selection criteria

Two investigators independently searched PubMed, EMBASE, and the Cochrane Library for relevant studies from inception to September 20, 2022 (search strategy in Supplementary material). We considered eligible RCTs comparing etomidate versus any comparator as an induction agent for endotracheal intubation in critically ill adults. We defined critically ill adults as patients undergoing emergency endotracheal intubation for critical illness, regardless of where the intubation was performed (e.g., prehospital, emergency department, intensive care unit). Critical illness was defined as a state of ill health with vital organ dysfunction and a high risk of imminent death if care is not provided [15]. We excluded pediatric patients aged <15 years old. We only included studies assessing a bolus dose of etomidate (as opposed to an infusion) to focus on the effect of etomidate as an induction agent during endotracheal intubation. We excluded non-randomized trials, systematic reviews, commentaries/editorials and literature reviews, and studies not addressing our review question. There was no language restriction. Two investigators independently assessed eligibility by screening the studies’ titles and abstracts after removing duplicates. The final selection of studies was based on full-text manuscripts. We resolved any disagreement through discussion under the supervision of one senior investigator.

2.2. Data collection and risk of bias assessment

Two investigators independently extracted data from included studies using a standardized data collection form. We resolved disagreements by consensus or by involving a third senior author. We collected data including first author, year of publication, country, study design, setting (hospital or other settings at enrollment), and primary and secondary outcomes. If there was a lack of data required for this meta-analysis or if the authors reported short-term mortality only, we contacted the first or corresponding author to request further information.

We assessed the risk of bias for randomized studies using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2) [16]. We assessed the overall certainty of the evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [17]. We prepared the GRADE evidence profile tables using the GRADEpro software. The presence of publication bias and small study effect for the primary outcome was investigated by visual estimation of the funnel plot.

2.3. Outcomes

The primary outcome was mortality at the main timepoint defined by trial authors, and the secondary outcome was the development of adrenal insufficiency.

2.4. Data analysis

Frequentist analyses were conducted using Review Manager version 5.4 [18]. We calculated risk ratios (RR) and 95% confidence intervals (CIs) using a Mantel-Haenszel fixed effects model. Heterogeneity was quantified by Tau² and I² statistics. I² values >50% were considered heterogeneous, and when present, we applied a random effect model (Mantel-Haenszel method). A P value <0.05 was considered statistically significant. Differences between subgroup estimates were considered significant for Pinteraction < 0.10. The number needed to harm (NNH) for the primary outcome was calculated using the following formula: NNH = 1/(weighted risk ratio of the etomidate arm – absolute risk ratio of the control arm). NNH is expressed as positive whole numbers, all decimals being rounded up.

We performed a sensitivity analysis for the primary and secondary outcome: studies comparing etomidate versus ketamine. In addition, we performed a sensitivity analysis for the primary outcome by assessing mortality at the longest follow-up available. We also performed the following exploratory subgroup analyses for the primary outcome: 1) excluding studies reporting only early death (<48 h after randomization), 2) including only studies where the number of patients with sepsis was more than half of the overall population, 3) excluding studies where the number of surgical patients was more than half of the overall population, 4) including only studies where the number of patients with baseline cardiovascular comorbidities was more than half of the overall population, 5) excluding studies with low mortality at the main timepoint defined by trial authors (<10% in the control arm), and 6) excluding studies with low mortality at the longest follow-up available (<10% in the control arm).

To contextualize and visualize the main finding, we used the relative risk and 95%CI for mortality and simulated 100,000 trials on the log scale, generated a representative probability density function on the risk ratio scale using kernel density estimation, and estimated the probability of any harm (RR > 1) and a number needed to harm ≤ 100 (RR ≥ 1.05) using STATA v.17 (STATACorp, College Station, USA).

We also performed a trial sequential analysis (TSA) [19,20] for the primary outcome with a diversity-adjusted information size calculated using a two-sided alpha of 0.05, a power of 80%, an anticipated relative risk increase of 20%, and a control event rate of 30%. We used the TSA Viewer software (Version 0.9 0.5 0.10 Beta. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

3. Results

Our search strategy identified a total of 4398 records. After screening, we included 11 randomized trials with 2704 critically ill adults (Fig. 1) [13,21-30] with major exclusions and reasons for exclusion detailed in Supplementary material: Table S1. The included studies were published between 1999 and 2022; eight were performed in the United States [13,22-24,26,27,29,30], one in the United Kingdom [21], one in France [25], and one in the Netherlands [28]. Comparators included: ketamine in four studies [13,25,27,30], midazolam in four [22-24,26], thiopental in one [21], ketamine plus midazolam in one [28], and ketamine and propofol admixture in one [29]. The dose of etomidate was between 0.2 and 0.3 mg/kg in most studies [13,22-28,30]. The characteristics of the included studies are summarized in Table 1. Among included studies, five were judged at low risk of bias, five at some concerns of bias, and the other at high risk of bias following RoB-2 evaluation (Supplementary material: Table S2). Although we requested the corresponding authors of the included studies for mortality data at a longer timepoint, we could not obtain any response.

Table 2 summarizes the outcome data. We found that etomidate
increased mortality at the main timepoint defined by trial authors (Fig. 2; 319/1359 [23%] vs. 267/1345 [20%]; RR = 1.16; 95% CI, 1.01–1.33; P = 0.03; I² = 0%; NNH = 31). Funnel plots showed no major asymmetry (Supplementary material: Fig. S1). This result corresponded to a 98.1% probability of any harm and a 92.1% probability that the number needed to harm was ≤100 (Fig. 3). In addition, TSA showed that the cumulative Z-curve crossed the required information size and statistical significance boundary, indicating that existing evidence was sufficient to conclude that etomidate increases mortality (Supplementary material: Fig. S2). According to the GRADE assessment, the certainty of the evidence for mortality at the main timepoint was deemed moderate (Supplementary material: Table S3).

The sensitivity analyses for mortality found consistent results with the main analysis (Supplementary material: Fig. S3–11). Among them, the statistically significant increased mortality was confirmed in patients randomized to receive etomidate when the comparator was ketamine, when excluding studies reporting only early death, when septic patients were the majority of the randomized patients, and when excluding studies with low mortality at the main timepoint defined by trial authors in the control arm (Supplementary material: Fig. S3, Fig. S6, Fig. S7, and Fig. S10). Magnitude and direction of the findings were confirmed when analyzing the mortality data at the longest follow up available, even if statistical significance was lost (Supplementary material: Fig. S4): 371/1359 [27%] vs. 339/1345 [25%]; RR = 1.07; 95% CI, 0.95–1.21; P = 0.27; I² = 0%) which corresponded to an 86.3% probability of any harm, and a 62.1% probability that the number needed to harm was ≤100 (Supplementary material: Fig. S5).

Different tests diagnosed adrenal insufficiency at different time points: adrenocorticotropic hormone (ACTH) stimulation test at three

Table 1
Characteristics of included studies in chronological order.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Journal</th>
<th>Country</th>
<th>Patients</th>
<th>Etomidate dose, mg/kg</th>
<th>Control</th>
<th>Mortality at the main timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abulom A, 1999</td>
<td>Anaesthesia</td>
<td>UK</td>
<td>Critically ill patients with ASA grade ≥ 3, with 2 or more organ failure, and requiring admission to ICU</td>
<td>N/A</td>
<td>Thiopental ICU</td>
<td></td>
</tr>
<tr>
<td>Schenarts CL, 2001</td>
<td>Acad Emerg Med</td>
<td>US</td>
<td>Patients requiring emergent or urgent intubation in the ED</td>
<td>0.3</td>
<td>Midazolam Hospital</td>
<td></td>
</tr>
<tr>
<td>Jacoby J, 2006</td>
<td>Ann Emerg Med</td>
<td>US</td>
<td>Patients requiring prehospital intubation</td>
<td>0.3</td>
<td>Midazolam Hospital</td>
<td></td>
</tr>
<tr>
<td>Hildreth AN, 2008</td>
<td>J Trauma</td>
<td>US</td>
<td>Adult trauma patients requiring intubation within 48 h after injury</td>
<td>0.3</td>
<td>Midazolam Hospital</td>
<td></td>
</tr>
<tr>
<td>Jahre P, 2009</td>
<td>Lancet</td>
<td>France</td>
<td>Adult patients requiring emergency intubation</td>
<td>0.3</td>
<td>Ketamine 28 days</td>
<td></td>
</tr>
<tr>
<td>Tekwani KL, 2010</td>
<td>Ann Emerg Med</td>
<td>US</td>
<td>Adults intubated in the ED with suspected infection</td>
<td>0.3</td>
<td>Midazolam Hospital</td>
<td></td>
</tr>
<tr>
<td>Driver B, 2014</td>
<td>Acad Emerg Med</td>
<td>US</td>
<td>Adult trauma patients receiving rapid sequence induction</td>
<td>0.3</td>
<td>Ketamine 30 days</td>
<td></td>
</tr>
<tr>
<td>Punt CD, 2014</td>
<td>Neth J Crit Care</td>
<td>Netherlands</td>
<td>Critically ill adult patients intubated in the ICU</td>
<td>0.2–0.3</td>
<td>Ketamine and midazolam 28 days</td>
<td></td>
</tr>
<tr>
<td>Smishney NJ, 2019</td>
<td>J Trauma Acute Care Surg</td>
<td>US</td>
<td>Adults admitted to the ICU, requiring emergent intubation</td>
<td>0.15</td>
<td>Ketamine and propofol 24 h</td>
<td></td>
</tr>
<tr>
<td>Powers WF, 2021</td>
<td>NCT03545503</td>
<td>US</td>
<td>Adults requiring rapid sequence induction in the prehospital or the ED</td>
<td>0.3</td>
<td>Ketamine 7 days</td>
<td></td>
</tr>
<tr>
<td>Matchett G, 2022</td>
<td>Intensive Care Med</td>
<td>US</td>
<td>Adults requiring emergency intubation</td>
<td>0.2–0.3</td>
<td>Ketamine 7 days</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ASA = American Society of Anesthesiologists, ED = emergency department, ICU = intensive care unit, N/A = not available, UK = United Kingdom, US = United States.

Table 2
Summary of primary and secondary outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of studies</th>
<th>Etomidate (mg/kg)</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at the main timepoint</td>
<td>11</td>
<td>319/1359 (23%)</td>
<td>267/1345 (20%)</td>
<td>1.16 (1.01–1.33)</td>
<td>0.03</td>
<td>0%</td>
</tr>
<tr>
<td>Comparison with ketamine</td>
<td>6</td>
<td>273/1201 (23%)</td>
<td>226/1198 (19%)</td>
<td>1.18 (1.02–1.37)</td>
<td>0.03</td>
<td>30%</td>
</tr>
<tr>
<td>Mortality at the longest follow-up</td>
<td>11</td>
<td>371/1359 (27%)</td>
<td>339/1345 (25%)</td>
<td>1.07 (0.95–1.21)</td>
<td>0.27</td>
<td>0%</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency, n (%)</td>
<td>6</td>
<td>147/695 (21%)</td>
<td>69/686 (10%)</td>
<td>2.01 (1.59–2.56)</td>
<td>&lt;0.001</td>
<td>0%</td>
</tr>
<tr>
<td>Comparison with ketamine</td>
<td>3</td>
<td>124/650 (19%)</td>
<td>65/649 (10%)</td>
<td>1.88 (1.46–2.42)</td>
<td>&lt;0.001</td>
<td>0%</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval
and five hours [29], at four hours [22], at four to six hours [24], at 24 h [21], random cortisol concentration or ACTH stimulation test at 48 h [25], and clinical diagnosis regardless of cortisol testing [13]. Etomidate was also associated with an increased risk of adrenal insufficiency (Supplementary material: Fig. S12: 147/695 [21%] vs. 69/686 [10%]; RR = 2.01; 95% CI, 1.59–2.56; P < 0.001; I² = 0%). Sensitivity analyses for adrenal insufficiency found similar results to the main analysis. (Supplementary material: Fig. S13).

4. Discussion

In this meta-analysis of randomized trials, we found a high probability that etomidate as an induction agent for endotracheal intubation increases mortality in critically ill patients. In addition, etomidate was associated with an increased risk of the occurrence of adrenal insufficiency.

Compared to the only meta-analysis that exclusively included randomized trials reporting no statistically significant difference in mortality [12], our meta-analysis includes additional recent randomized trials and demonstrates that the mortality increase with etomidate is statistically significant. Among recent trials, a large, high-quality, randomized trial reported increased mortality in the etomidate arm [13] which increases the confidence that the harm signal with etomidate is accurate and robust. Specifically, there is a 98.1% probability that etomidate increases mortality and a 92.1% probability that it does so in a clinically significant manner (NNT ≤100).

We evaluated etomidate exclusively as an induction agent for endotracheal intubation. A previous meta-analysis demonstrated that the risk of adrenal insufficiency by etomidate was more pronounced in the earlier phase than in the later phase [12]. Given the adverse impact of adrenal insufficiency on hemodynamic conditions, etomidate likely influences short-term mortality, while long-term mortality might be less affected, as suggested by our findings.

We also observed an increased risk of adrenal insufficiency, a consistent finding with the prior meta-analyses [10,12]. The international guidelines for adrenal insufficiency in critically ill patients state that no single criterion is sufficient for a definitive diagnosis due to its complex pathology, although there are different methods to measure adrenal function [31]. This meta-analysis also found substantial heterogeneity concerning the timing of assessment or diagnostic methods among the studies reporting adrenal insufficiency. Nonetheless, all the studies reporting adrenal insufficiency showed an increased risk in the etomidate arm, which confirms the adverse effect of etomidate on adrenal function. Therefore, we argue that the harm of etomidate is related to reduced responses to stress in the intermediate term rather than immediate or acute reactions soon after drug administration.

We believe the mortality increase with etomidate demonstrated in this meta-analysis implies that clinicians should consider an alternative induction agent for intubation in critically ill patients. The current international guidelines suggesting etomidate as a sedative drug for rapid
sequence intubation [4,5] should be revised accordingly. Replacing etomidate with currently available alternatives (e.g., ketamine) would save a substantial number of critically ill patients undergoing endotracheal intubation, given the NNH of 31 and the widespread use of etomidate [3].

Future research should address the optimal strategy of induction agents in critically ill patients. Ketamine and propofol are the two hypnotics commonly used for rapid sequence induction. However, there is no randomized trial comparing the two drugs in intensive care settings, probably because of their different effects on hemodynamic status. A prediction score to stratify the risk of post-intubation hypotension could also be used for patient selection in future trials [32].

The inclusion of only randomized trials is a strength of our meta-analysis. Furthermore, with several recently published studies, we included three times more patients than in the previous meta-analysis [12]. The conceptualizing of the findings using a probability-based approach allowed us to demonstrate the high probability of both short- and long-term mortality increases by etomidate. The sensitivity analyses and trial sequential analysis also confirmed the association of etomidate with harm, suggesting these findings are definitive.

We should acknowledge several limitations. First, violations of assigned protocol could cause bias in the pooled results. For example, in a study comparing etomidate with ketamine, patients assigned to etomidate could receive both etomidate and ketamine because of inadequate sedation. Such violations could generate bias toward the null. Second, we included studies assessing any induction agent other than etomidate as a control, which could introduce heterogeneity. However, overall statistical heterogeneity was 0%, suggesting that the harm of etomidate would be consistent regardless of the type of comparators.

5. Conclusions

This meta-analysis found a high probability that etomidate increases mortality when used as an induction agent in critically ill patients with a number needed to harm of 31.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors’ contribution

YK, GP, GMa, SF, ST, Gmo, AZ, TCL, and GL conceived the study. YK, GP, GMa, and GL did the literature search. YK, GP, GMa, and GL did the statistical analysis. YK, GP, GMa, and GL wrote the initial protocol. YK, GP, GMa, SF, ST, Gmo, AZ, TCL, and GL wrote the manuscript. All authors shared the study data, gave a critical appraisal of the protocol, provided crucial revisions, and approved the final manuscript.

Funding

Dr. Yuki Kotani receives support from the Uehara Memorial Foundation. Dr. Todd Lee receives research salary support from the Fonds de recherche du Québec – Santé. The funding agencies had no role in the study design; collection, management, analysis, and interpretation of data; writing of the report, or the decision to submit the report for publication.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

We collected the summary data from published randomized trials. All the data generated or analyzed for this study are included in this published article and its supplementary file. Further information is available from the corresponding authors upon reasonable request.

Acknowledgments

The authors wish to thank all the patients and investigators of the included papers. We also thank Dr. Jacqueline Hannam for providing detailed data on the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154317.

References


