SYSTEMATIC REVIEW

Etomidate Compared to Ketamine for Induction during Rapid Sequence Intubation: A Systematic Review and Meta-analysis

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Abstract

Aims and objectives: The objective of the study was to compare the safety and efficacy of etomidate and ketamine as induction agents for rapid sequence intubation (RSI) in acutely ill patients in emergency department and prehospital settings with respect to post-induction hypotension and first-pass intubation success during RSI.

Materials and methods: For this systematic review and meta-analysis, we searched PubMed, Embase, Cochrane, and ClinicalTrials.gov between database inception and June 1, 2021. Articles were included if they compared safety and efficacy of etomidate vs ketamine as induction agents, in patients undergoing RSI in emergency department and prehospital settings, without any restrictions on study design. The outcome measures were incidence of post-induction hypotension and first-pass intubation success. The dichotomous outcomes were assessed for odds ratio (OR) with 95% confidence interval (CI) using random-effects meta-analysis.

Results: Of 87 records identified, 9 were eligible, all assessed as having a low to moderate risk of overall bias. Six studies, including 12,060 patients from prehospital emergency medical services, air medical transport, and emergency department settings, compared post-induction hypotension incidence between etomidate and ketamine groups. The meta-analysis showed that etomidate was associated with decreased risk of post-induction hypotension compared to ketamine (OR: 0.53; 95% CI: 0.31–0.91; $I^2 = 68\%$). Seven studies, including 15,574 patients, reported on the rate of first-pass intubation success with etomidate vs ketamine. In the pooled analysis, no differences were seen in first-pass intubation success during RSI using etomidate vs ketamine as the induction agent (OR: 1.13; 95% CI: 0.95–1.36; $I^2 = 16\%$).

Conclusion: The use of etomidate for induction during RSI is associated with a decreased risk of post-induction hypotension as compared to the use of ketamine, without an impact on the first-pass intubation success rate.

Keywords: Airway management, Endotracheal intubation, Etomidate, Intravenous anesthetics, Ketamine, Rapid sequence intubation.

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Introduction

Rapid sequence intubation (RSI) is the concurrent administration of an induction agent and a neuromuscular blocker for facilitating endotracheal intubation. Bag-valve-mask ventilation is avoided during the interval between administration of induction medications and endotracheal tube placement, thus preventing gastric insufflation and reducing the risk of aspiration. While RSI results in increased first-pass success (successful endotracheal tube placement on the first attempt) and reduced incidence of aspiration, the induction agents are associated with the risk of hypotension in critically ill patients. The selection of induction agents is a critical consideration during RSI in acutely ill patients.

Etomidate and ketamine are commonly used as induction agents in patients undergoing RSI. Etomidate is an imidazole-derived anesthetic agent that blocks neuroexcitation by acting on the gamma aminobutyric acid (GABA) receptor complex. Ketamine is a dissociative anesthetic drug that results in neuroinhibition by acting as an antagonist of the N-methyl-D-aspartate (NMDA) receptor. The choice of induction agent may have an impact on the success of the procedure and hemodynamic parameters. No comprehensive review is available of the evidence regarding the impact of the choice of induction agent for RSI on the success of the procedure and hemodynamic stability with the use of different induction agents. The current review was undertaken to inform emergency physicians on the choice of the induction agent for RSI based on the available evidence. The purpose of this review was to evaluate whether there was an association between the use of etomidate vs ketamine as induction drugs for RSI, with hemodynamic or clinical (definitive airway) end points.

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Aims and Objectives

The primary objective of the systematic review and meta-analysis was to compare the safety of etomidate vs ketamine as induction agents for RSI for critically ill patients with respect to post-induction hypotension in emergency department and prehospital settings. The secondary objective was to evaluate these two induction agents for efficacy with respect to first-pass intubation success during RSI.

Eligibility Criteria

Articles were included if they compared safety and efficacy of etomidate vs ketamine as induction agents, in patients of all age groups undergoing RSI in the emergency department and prehospital settings. There were no restrictions on study design. Articles were excluded if they compared combinations of two or more induction agents (for instance, "ketamine + propofol" vs "etomidate + fentanyl").

Outcomes

The outcome measures were the incidence of post-induction hypotension and first-pass intubation success (successful placement of endotracheal tube on the first laryngoscopy attempt).

Information Sources

The principal investigator (SCS) designed and conducted a comprehensive search of the following databases and trial registers—PubMed, Embase, Cochrane, and ClincalTrials.gov up to and including June 1, 2021. The search strategy used controlled vocabulary as follows: (a) Medical Subject Headings in PubMed—("Intubation, Intratracheal" [Mesh]) AND "Etomidate" [Mesh]) AND "Ketamine" [Mesh]; (b) Embase—"endotracheal intubation"/mj AND "ketamine"/mj AND "etomidate"/mj; (c) Cochrane—etomidate in Title Abstract Keyword AND ketamine in Title Abstract Keyword AND intubation in Title Abstract Keyword; and (d) ClinicalTrials.gov—Ketamine etomidate|Completed Studies|Studies With Results|intubation. The search strategy was limited to the English language studies, and all studies published in the databases since their inception were included. In phase I, the investigators (SCS and MSB) screened all titles and abstracts. In phase II, records considered potentially relevant were assessed in full text for eligibility (SCS and MSB).

Data Analysis

Relevant data were extracted—citation details, the study site (prehospital emergency medical services or emergency department), retrospective or prospective study, observational or interventional study, treatment assignment mechanism, the intervention details of the induction agent, and outcomes of interest. One investigator (SCS) entered the data into the Review Manager program. Another investigator (MSB) checked this for accuracy. We assessed the risk of bias in the following domains: (a) the randomization process; (b) blinding of participants and personnel; (c) blinding of outcome assessment; (d) missing outcome data; and (e) selective reporting of the results.[1] The quality of evidence was evaluated with the Oxford Centre for Evidence-Based Medicine Levels of Evidence document and graded levels from 1 (high quality) to 5 (low quality).[2]

Eligible outcomes were post-induction hypotension and first-pass intubation success rate. The eligible studies excluded patients with preinduction hypotension (systolic blood pressure <100 mm Hg prior to the administration of induction agents). Any measurement of post-induction hypotension was eligible for inclusion, but the measurement time point (including baseline vital signs) was considered when interpreting the study results and in determining which outcomes were similar enough to combine for synthesis. Wherever multiple outcomes were reported, one outcome was selected for inclusion in analyses, selecting the result that provided the most relevant information for analysis (e.g., post-induction hypotension at ≤1 hour after RSI). Measurement of immediate post-induction hypotension was prioritized (≤1 hour after procedure), over delayed hypotension (e.g., hypotension at any time point during 24 hours).

We pooled the data from emergency department and prehospital emergency medical services studies for a better understanding of the comparative outcomes with the use of etomidate vs ketamine as induction agents for RSI in an emergency setting. We used RevMan (Review Manager computer program, version 5.4, The Cochrane Collaboration, 2020) for meta-analyses. Dichotomous outcomes were assessed for odds ratio (OR) with 95% confidence interval (CI) using Mantel–Haenszel (M-H), random-effects model to account for the clinical and statistical heterogeneity between studies. p <0.05 indicated statistical significance. The heterogeneity was evaluated by using statistical tests for heterogeneity variance (τ^2) and inconsistency (I^2), and by visual inspection of forest plots. Heterogeneity was deemed significant if I^2 >50%.

Results

We found 87 records in database and trial registry search (Flowchart 1). After the removal of duplicates and screening titles, we screened abstracts of 27 records, from which we reviewed 15 full-text articles, and ultimately included 9 studies (Table 1). We collected the outcome data from eight published reports and one report of study results of a randomized controlled trial (RCT) from the ClinicalTrials.gov registry. Out of the nine, six studies contained data for post-induction hypotension and seven studies contained data for first-pass intubation success.

We excluded six studies from our review—Mudri et al.,[3] Groth et al.,[4] Upchurch et al.,[5] Jabre et al.,[6] Van Berkel et al.,[7] and Mohr et al.[8] We excluded studies by Upchurch et al.[5] and Jabre et al.,[6] because in these studies, first-pass intubation success and post-induction hypotension were not assessed. Mudri et al.[3] and Groth et al.[4] reported first-pass success and hypotension for all patients undergoing RSI as a single group, rather than for individual induction agents. Van Berkel et al.[7] excluded patients if they did not survive 24 hours post-intubation—an outcome directly related to post-induction hypotension and first-pass intubation success, introducing the high risk of reporting bias. Finally, the patients enrolled in the study by Mohr et al.[8] were a subset of

Flowchart 1: Flow diagram of systematic database search

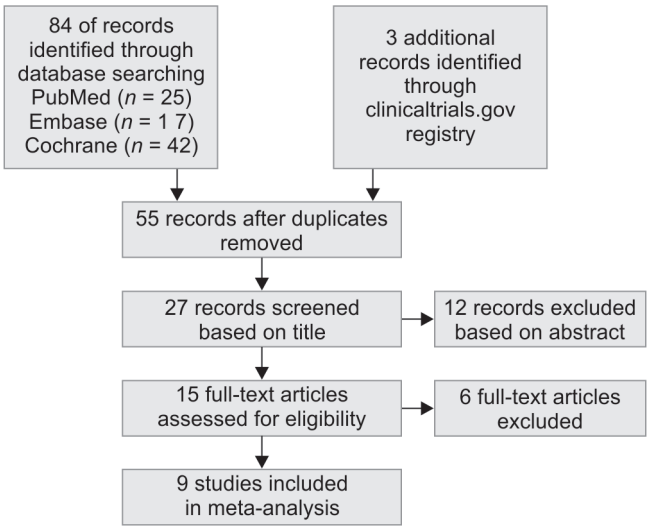

Table 1: Characteristics of included studies

					Interventions		Outcomes		
Author (year)	*Study design*	*Country*	*Sample size*	*Source of participants*	*Etomidate*	*Ketamine*	*First-pass success*	*Hypotension*	*Level of evidence**
April et al. (2020)[9]	Retrospective, observational	USA	6,806	Emergency department	✓	✓	✓	✓	3
Driver (2019)[10]	Randomized controlled trial	USA	143	Emergency department	✓	✓	✓	✓	2
Farrell et al. (2020)[15]	Retrospective, observational	USA	82	Emergency department	✓	✓	✓	X	3
Nakajima et al. (2019)[11]	Randomized controlled trial	USA	68	Emergency department	✓	✓	X	✓	2
Patanwala et al. (2014)[16]	Retrospective, observational	USA	2,098	Emergency department	✓	✓	✓	X	3
Pollack et al. (2020)[12]	Retrospective, observational	USA	7,466	Air medical transport	✓	✓	✓	✓	3
Price et al. (2013)[13]	Retrospective, observational	USA	100	Air medical transport	✓	✓	✓	✓	3
Sivilotti et al. (2003)[17]	Prospective, comparative	USA	3,407	Emergency department	✓	✓	✓	X	3
Stanke et al. (2018)[14]	Retrospective, observational	USA	113	Prehospital emergency medical service	✓	✓	X	✓	3

*Evaluated according to the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence document with levels from 1 (high quality) to 5 (low quality)[2]

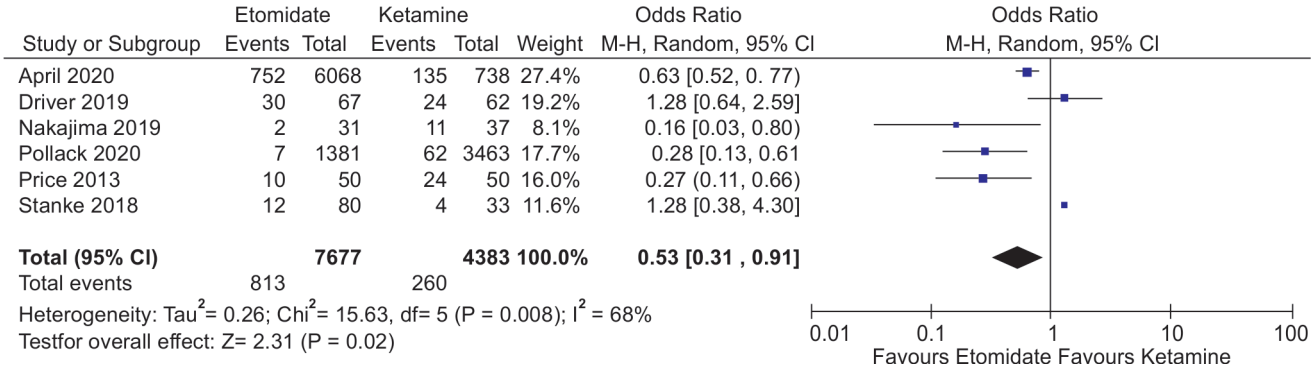

Fig. 1: Forest plot for post-induction hypotension with the use of etomidate ($n = 7,677$) vs ketamine ($n = 4,383$) during RSI

the patients enrolled in the National Emergency Airway Registry used for data collection over the same time period by April et al.[9]

Six studies including four retrospective studies and two RCTs compared the incidence of post-induction hypotension between etomidate and ketamine groups (Fig. 1).[9–14] These studies enrolled 12,060 patients in prehospital emergency medical services, air medical transport, and emergency department settings. These six studies were pooled, as they each identified the incidence of post-induction hypotension with the use of etomidate vs ketamine as the induction agent during RSI. Etomidate use was associated with a significantly decreased risk of post-induction hypotension compared to ketamine (OR: 0.53; 95% CI: 0.31–0.91; $p = 0.02$), with significant heterogeneity ($I^2 = 68\%$; $p = 0.008$).

Seven studies, including a total of 15,574 patients from prehospital emergency medical services, air medical transport, and emergency department settings, reported on the rate of first-pass intubation success during RSI using etomidate vs ketamine as the induction agent (Fig. 2).[9,10,12,13,15–17] Meta-analysis of outcomes of these seven studies showed no difference in first-pass intubation success during RSI using etomidate vs ketamine as the induction agent (OR: 1.13; 95% CI: 0.95–1.36; $p = 0.17$), without significant heterogeneity ($I^2 = 16\%$; $p = 0.31$). A graphical summary of the risk of bias evaluations is provided in Figure 3. In terms of the overall risk of bias, all the included studies had a low to moderate risk of bias, but none of these had a high risk of bias.

Discussion

The avoidance of adverse events during RSI and successful intubation of acutely ill patients on the first attempt can be influenced by operator-related factors, selection of airway

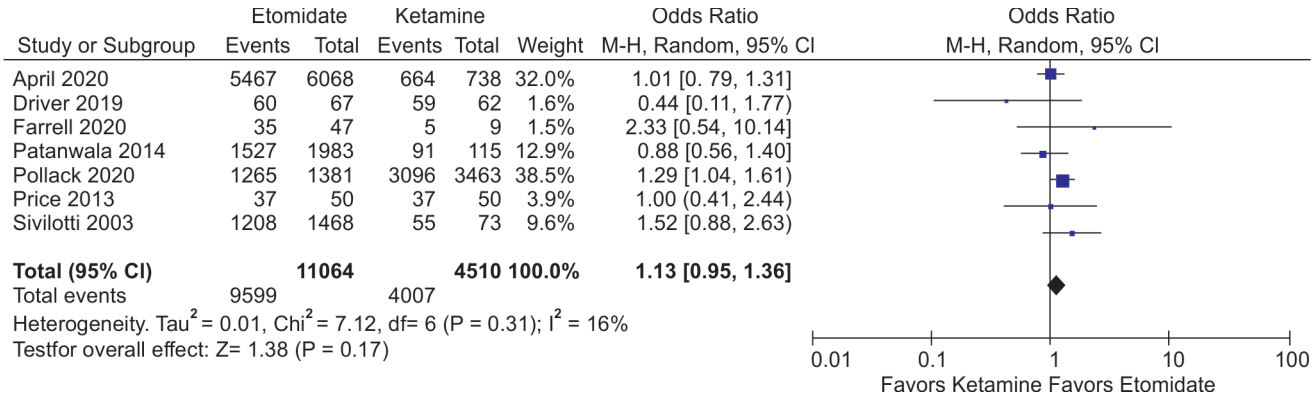

Fig. 2: Forest plot for first-pass success of endotracheal intubation with etomidate ($n = 11,064$) vs ketamine ($n = 4,510$) during RSI

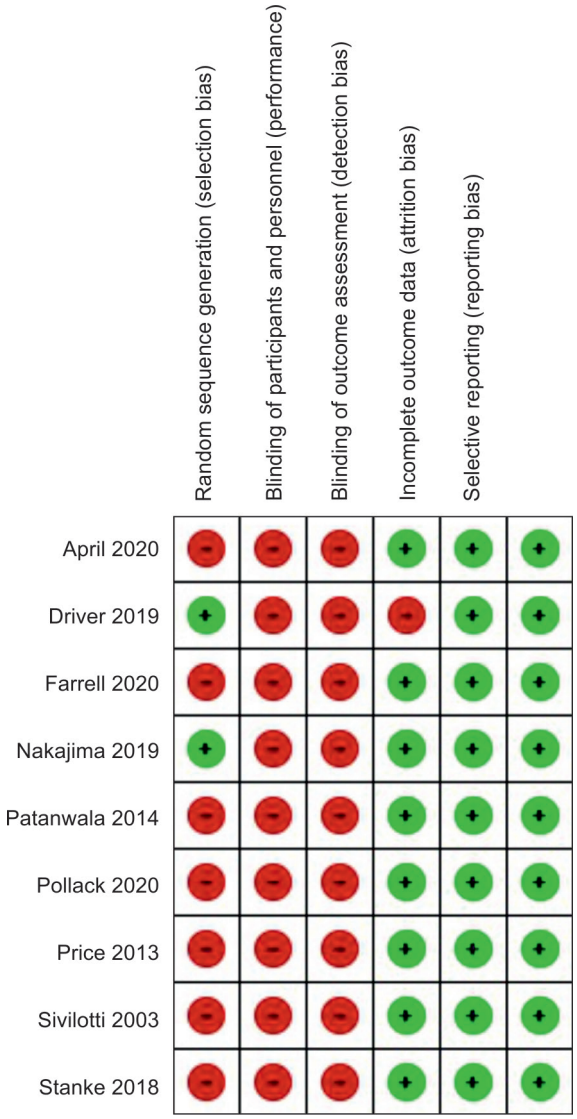

Fig. 3: Risk of bias summary for included studies

equipment, and choice of medications;[18] hence, the choice of induction drug is dictated by hemodynamic considerations.[19] This is the first systematic review and meta-analysis to compare the safety and efficacy of etomidate and ketamine as induction agents for RSI with respect to post-induction hypotension and first-attempt intubation success in prehospital and emergency department settings. The certainty of evidence from this meta-analysis is considered moderate, because of the concerns for bias due to the largely observational nature of the included studies.[20] The results of the meta-analysis favor etomidate for a significant reduction of post-induction hypotension compared to those of ketamine during RSI in acutely ill patients. This result is especially striking and important, as recent consensus guidelines[19] favor the use of ketamine in critical patients for hemodynamic stability and ketamine use has increased over time. Ketamine has an indirect sympathomimetic effect due to reuptake inhibition of endogenous catecholamines; however, it also has a direct myocardial depressant effect that may decrease ventricular contractility in critically ill patients.[21] It has been suggested that the negative inotropic action of ketamine may outweigh the sympathomimetic effects in patients who have depleted catecholamine reserves.[22] However, the result came with significant heterogeneity between the studies. This was primarily due to the results of Driver[10] and Stanke et al.,[14] which showed no significant difference in the hemodynamic outcome data between the two groups. The sample sizes for both these studies were small and therefore not powered to detect significant differences in the hemodynamic data between the groups. For Driver 2019, the only available data were interim results from the trial registry, making comparison with other studies difficult. Another important consideration is the successful placement of endotracheal tube on the first laryngoscopy attempt during RSI to prevent aspiration and reduce the risk of hypoxia. First-attempt intubation success is desirable because complications increase as the number of intubation attempts increases. Previous studies have largely focused on the effects of neuromuscular blocking agents.[23] Nevertheless, the sedative drug used can affect this outcome by various potential mechanisms, for example, the response to the noxious intubation stimulus, and the time of onset of neuromuscular blockade can be modified by the induction agent.[24,25] Sivilotti et al. assessed the effect of various induction agents on intubation success in a multicenter study and found that collectively, propofol, thiopentone, and methohexital were associated with improved first-attempt intubation success, compared to other induction agents such as ketamine, etomidate, and benzodiazepines.[17] They suggested that the former group of anesthetic agents produce a deeper plane of anesthesia, thus facilitating intubation before neuromuscular blockade is

achieved by paralytics alone. But these former agents are rarely used for emergency intubation because of a higher risk of adverse effects such as hypotension. This meta-analysis builds on the findings of these previous studies by focusing on ketamine and etomidate, two of the most frequently used induction agents due to their comparatively favorable hemodynamic profile. However, it is possible that there are additional confounding variables such as difficult airway score of the patient, experience of the intubating physician, and use of difficult airway aids such as video laryngoscopes that were not included in the meta-analysis. The meta-analysis showed no significant difference between the rates of first-pass intubation success during RSI using etomidate vs ketamine as the induction agent. This result potentially reflects that both agents provide similarly adequate intubating conditions and allow timely placement of a definitive airway in acutely ill patients, in line with the goal of RSI.

Limitations

The studies included predominantly retrospective studies and only two RCTs (for one RCT, only trial registry data were available).[10] The included studies were limited by selection bias, relatively small sample sizes, and lack of blinding of personnel and outcome assessment.

Conclusion

Findings from the meta-analysis suggest that the use of etomidate is associated with decreased risk of post-induction hypotension during RSI compared with ketamine, while the choice of induction agent has no effect on first-pass intubation success. This provides important evidence for hemodynamic stability of etomidate compared to ketamine for acutely ill patients requiring endotracheal intubation. However, our understanding of the impact of the choice of induction agents for RSI would further benefit from future high-quality blinded RCTs that make direct comparisons between the induction agents in combination with particular paralytic agents.

Author Contributions

The study was conceived and designed by SCS. SCS and MSB searched and reviewed the articles for eligibility and extracted the data. SCS performed the statistical analysis and drafted the manuscript, and MSB contributed to its revision. SCS takes the responsibility for the paper as a whole.

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