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Review Article

The Role of Etomidate for Rapid Sequence Intubation in Emergency Medicine: A Systematic Review

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ABSTRACT

Background: Etomidate, a short-acting hypnotic drug, plays a pivotal role in induction for intubation, particularly in emergency settings. Its favourable hemodynamic profile renders it a suitable choice for patients with hemodynamic instability

Methods: In this systematic review, we aim to delineate its role in emergency ward settings. Through a systematic search across databases, we identified nine eligible studies for inclusion. We searched the databases of PubMed, Scopus, ProQuest, and Medline (Ovid) from 2004 to 2023 for Randomized Controlled Trials (RCTs) and observational studies in which the study population was referred to the emergency department and received etomidate for Rapid sequence intubation (RSI).

Results: These studies collectively underscored the safety and efficacy of etomidate in emergency patients, with its suppressive effects on the adrenal axis deemed clinically insignificant.

Conclusion: The rapid onset of action and favourable hemodynamic profile position etomidate as a desirable agent for rapid sequence induction. However, further studies are warranted to strengthen recommendations in this regard.

Introduction

Rapid sequence induction/intubation (RSI) stands as the gold standard for airway management and securing airways within the emergency department (ED), particularly in critically ill patients [1-2]. Etomidate, a short-acting hypnotic drug, shares pharmacological similarities with gamma-aminobutyric acid (GABA). With its rapid onset of action, typically within five to 15 seconds, and a duration of effect up to 15 minutes, etomidate has gained prominence as an induction agent for intubation [3-4]. Its extensive distribution volume of five liters, coupled with high lipid solubility, facilitates rapid brain penetration within one minute of administration. Metabolized primarily by the liver, etomidate exhibits minimal hemodynamic effects, making it an attractive choice, especially in hemodynamically unstable patients. While common side effects include injection pain, hiccups, nausea, vomiting,

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myoclonus, and adrenal suppression, none are deemed clinically significant [5-7]. The potential for adrenal insufficiency following etomidate administration, attributed to 11-beta hydroxylase suppression, remains theoretical and warrants further investigation [8-9]. The aim of this study is to comprehensively review the clinical evidence regarding the use of etomidate in emergency medicine, providing insights for emergency medicine specialists and anesthesiologists.

Methods

Search strategy and selection criteria:

A systematic search of the PubMed database was conducted using predefined search terms encompassing emergency department settings, etomidate, and rapid sequence induction. The PICO criteria were employed to refine the search strategy, focusing on patients requiring intubation, etomidate as the intervention, with no comparison, and outcomes related to etomidate's side effects in RSI. We used the following search strategy for searching PubMed data base: ('emergency ward'/exp OR 'emergency department':ti,ab OR 'emergency room':ti,ab OR 'emergency unit':ti,ab OR 'emergency ward':ti,ab OR 'emergency health service'/exp OR 'accident service':ti,ab OR 'accident squad service':ti,ab OR 'emergency center':ti,ab OR 'emergency centre':ti,ab OR 'emergency dispensary':ti,ab OR 'emergency health care service':ti,ab OR 'emergency health service':ti,ab OR 'emergency healthcare service':ti,ab OR 'emergency medical service':ti,ab OR 'emergency medical services':ti,ab OR 'emergency medical tags':ti,ab OR 'emergency service':ti,ab OR 'trauma center':ti,ab OR 'trauma centers':ti,ab OR 'triage':ti,ab OR 'emergency medicine'/exp OR 'emergency medicine':ti,ab OR 'emergency medical':ti,ab) AND ('etomidate'/exp OR 'amidate':ti,ab OR 'ethomidate':ti,ab OR 'etomidat lipuro':ti,ab OR 'etomidate':ti,ab OR 'hypnomidate':ti,ab) AND ('rapid sequence induction'/exp OR 'rapid sequence induction':ti,ab OR 'rapid sequence induction and intubation':ti,ab OR 'rapid sequence intubation':ti,ab)

Inclusion and eExclusion criteria:

Only clinical trials and observational studies investigating etomidate in RSI were considered for inclusion. Non-clinical trial studies and observational studies and also articles in languages other than English were excluded.

Data collection, extraction, and evaluation of article quality:

Following database extraction, articles underwent three-stage screening, including title screening, abstract review, and full-text assessment. Two independent researchers evaluated the remaining articles for quality and risk of bias using the JADAD checklist. Discrepancies were resolved by a third researcher, with decisions based on majority consensus.

Results

The initial database search yielded 1557 studies, of which 526 were excluded due to duplication. Following title and abstract screening, 142 studies entered the full-text review stage, with nine studies deemed eligible for inclusion (Figure 1). These studies, published between 2004 and 2023, predominantly focused on adult populations. While methodological heterogeneity precluded meta-analysis, findings from individual studies underscored etomidate's safety and efficacy in emergency settings. The characteristics of the studies are showed in (Table 1). Because of different methods of these studies, a meta-analysis was not possible.

Table 1- General characteristics and results of eligible studies

No	Authors	Location	Studies	Samples	Conclusion
1	Güniz Meyancı Köksal, M.D	Turkey	prospective, randomized, clinical trial	60	Etomidate has a good hemodynamic profile and can be used as first choice in hemodynamically unstable patients
2	Peter J. Zed, BSc, BSc(Pharm), PharmD, FCSHP	Canada	prospective observational study	522	Etomidate is a good choice in unstable patients due to its hemodynamic profile
3	Patricia Jabre	France	prospective, randomised, controlled, single-blind (caregiver) trial	469	A bollos dose of etomidate is not associated with higher risk of mortality in comparison to ketamine
4	Y F Choi	Hong Kong	prospective observational study	160	Etomidate provides suitable conditions for intubation in patients undergoing rapid sequence intubation in emergency situations.

5	Amy N. Hildreth, MD	USA	prospective, randomized, controlled, nonblinded study	30	Etomidate can cause adrenal suppression in traumatic patients underwent RSI
6	Kenny V. Banh, MD, FACEP	USA	retrospective chart review	1322	No harm was detected due to adrenal suppression in patients underwent RSI with etomidate
7	Cameron P. Upchurch	USA	retrospective analysis of data collected	968	Etomidate and ketamine had same outcome in mortality rate
8	Knak SKS	USA	Prospective, single-center, randomized parallel-group trial	143	There is no different between etomidate and ketamine regarding to post intubation SOFA, ICU outcome, or mortality.
9	Srivilaithon W	Thailand	Prospective, randomized, controlled, single-blind trial	260	There is no statistically significant difference between etomidate and ketamine in septic patients early or late survival. Septic patients who received etomidate have higher chance to need vasopressor support.

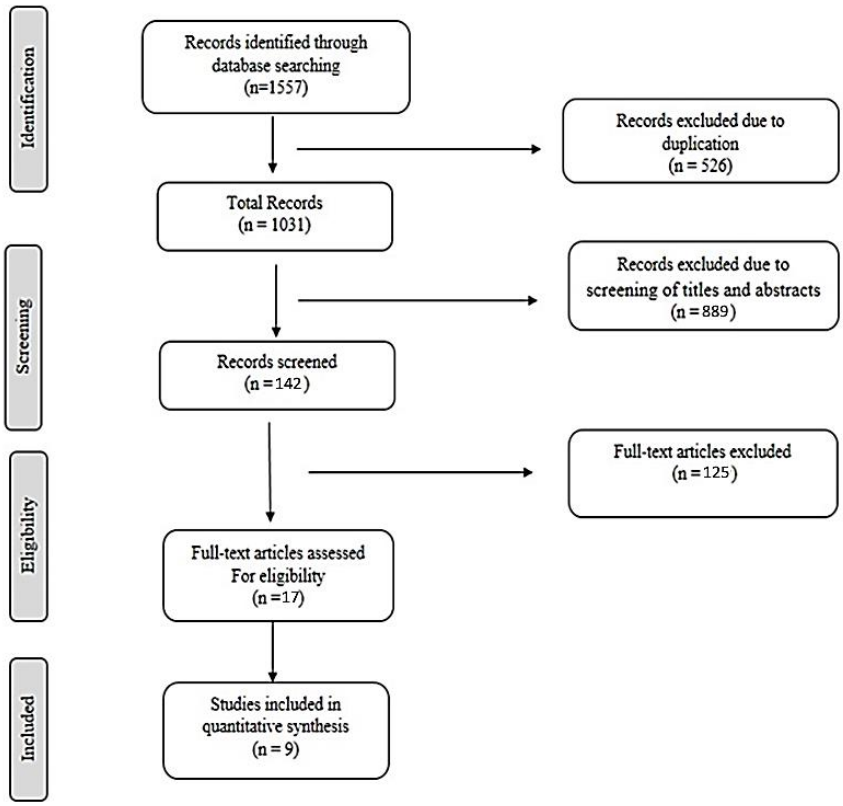

Figure 1- Flow diagram of studies for inclusion in the systematic review

Güniz Meyancı Köksal et al. [1]:

Sixty patients in three groups were studied. Aim of study was comparing three different regimens of administration of etomidate for RSI on hemodynamic status and cortisol levels in patients. group I received a single dose of etomidate, group II received methylprednisolone after administration of etomidate and in group III patients underwent RSI only by administration of midazolam.

All groups had a lower cortisol level after 4 hours of intubation (respectively $p<0.001$, $p=0.021$ and p-0.043 in groups I to III). After 24 hours, group I had a lower cortisol level than pre-intubation levels and there was a rise in cortisol levels in groups II and III. This rise was statistically significant in comparison to pre-intubation levels only in group III ($p=0.008$). Patients in group I had

a significant lower cortisol level after 4 hours in comparison to other two groups. These lower levels remain for 24 hours after intubation in comparison to groups II and III. Compared within the group, the 4-hour SOFA scores of groups I and III were lower than the initial values.

Peter J et al. [2]:

In a period of 42 months, 522 patients underwent RSI using etomidate as induction agent. There was a significant increase in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) just after intubation. After five minutes of intubation SBP was still higher than base line although DBP and HR returned to their base line levels.

In a subgroup with 80 patients who had pre-intubation hypotension with a SBP under 100 mmHg, there was an increase in both SBP and DBP after induction. No changes in HR have been detected in this subgroup.

Adverse effects within 15 minutes after etomidate administration included cardiac arrest (n = 17), vomiting (n = 5), myoclonus (n = 3), and bradycardia (n = 2). All patients enrolled in this study were successfully intubated.

Patricia Jabre et al. [3]:

Four hundred and sixty-nine patients in two groups have been studied (234 patients in etomidate group and 235 patients in ketamine group). There was no statistically significant difference in SOFA score and Δ-SOFA score between two groups. In addition, none of the six components of the SOFA score were significantly different between the etomidate and ketamine groups. No differences have been found in intubation difficulty or adverse outcomes. Although there was a lower cortisol level in etomidate group, mortality was not different between two groups. furthermore, there was no difference in length of stay in the intensive care unit, 28-day mortality, extubating time or days without mechanical ventilation on day 28.

Y F choi et al. [4]:

One hundred and sixty patients studied in two groups. seventy-seven patients received midazolam as induction agent and 83 patients received etomidate. In midazolam group a 10% reduction in mean SBP observed in patients five minutes after intubation. No significant reduction of mean SBP observed in etomidate group.

Amy N. Hildreth et al. [5]:

Thirty patients studied in two groups. eighteen in etomidate group and twelve in fentanyl-midazolam group. Patients in etomidate group had significantly lower cortisol level after intubation and had lower response to corticotropin stimulation test. These patients had significantly longer hospital length of stay and longer ventilatory support time and needed more blood transfusion in comparison to patients in fentanyl-midazolam group.

Kenny V et al. [6]:

A total number of 1325 patients studied in two groups. 443 patients received higher etomidate dose for intubation and 882 patients underwent induction with a lower etomidate dose. All patients were traumatic patients. Study showed no significant difference in mortality, hospital lent of stay or ICU days but a significant increase in episodes of hypotension found in limited etomidate group.

Cameron P et al. [7]:

Study included 968 patients in two groups (526 patients in etomidate group and 442 patients in ketamine group). Although there was a lower sepsis rate in ketamine group, mortality rate and peri intubation adverse events were same in two groups. First attempt intubation success, need for surgical airway and peri-intubation cardiac arrest rate were same in both groups.

Knak et al. [10]:

In a single-center, randomized, parallel-group trial, Knak et al. studied 143 patients. They studied SOFA score as the primary outcome. Patients divided in etomidate group and ketamine group, randomly. The incidence of post-intubation hypotension was 28% in the ketamine group vs. 26% in the etomidate group, which did not demonstrate a statistically significant difference. They, also, did not found any significant difference among two groups in ICU outcomes or mortality rate.

Srivilaithon et al. [11]:

This study included 260 septic patients divided in two groups randomly. Etomidate-group patients received 0.2-0.3 mg/kg etomidate and ketamine-group patients received 1-2 mg/kg ketamine. Researchers defined survival outcomes and adverse effects as primary outcome of study. The study did not show a statistically difference between two groups in 24-hour mortality, 7-days mortality, and 28-days mortality. Etomidate-group patients had a significantly higher need for vasopressors.

Discussion

Our systematic review delves into the efficacy and safety of etomidate as a hypnotic agent for rapid sequence induction (RSI) in the emergency department (ED). Despite the fundamental role of RSI in securing the airway and managing critically ill patients, the available literature on the specific use of etomidate in this context remains limited. Several key findings emerge from the

studies included in our review. Firstly, etomidate demonstrates a consistent profile of rapid onset of action and short duration of effect, aligning with its pharmacokinetic properties. This characteristic makes it an attractive option for RSI, particularly in situations necessitating prompt airway management in hemodynamically unstable patients.

A notable observation from our review is the varied impact of etomidate on cortisol levels across different studies. While some studies reported a decrease in cortisol levels post-administration, none demonstrated a significant alteration in mortality rates. However, caution is warranted in interpreting these findings, particularly in light of the small sample sizes in certain studies and the absence of randomization in patient selection.

Furthermore, the inclusion of studies without control groups underscores the need for further research to elucidate the comparative efficacy and safety of etomidate in RSI. Despite this limitation, studies such as those by Peter J et al. And Güniz Meyancı Köksal et al. underscored the favorable outcomes associated with etomidate administration, irrespective of the specific regimen employed.

Interestingly, our review highlights the lack of consensus regarding the optimal dosing strategy for etomidate in RSI. While some studies explored different administration regimens, none demonstrated a clear advantage in dose reduction. This suggests that the standard dosing protocol remains appropriate, emphasizing the need for consistency in practice guidelines.

Moreover, the absence of control groups receiving alternative hypnotic agents, such as propofol or thiopental, underscores a notable gap in the existing literature. Future research endeavors should aim to address this gap by conducting controlled trials comparing etomidate to other commonly used induction agents in RSI.

Conclusions

In conclusion, etomidate emerges as a promising agent for RSI in the ED, offering rapid onset of action and a favorable hemodynamic profile. However, the scarcity of high-quality evidence underscores the need for further research to inform clinical practice guidelines and optimize patient outcomes in emergency airway management. Through rigorous investigation and comparative studies, the optimal use of etomidate in RSI can be delineated, ultimately enhancing the standard of care for critically ill patients in the emergency setting.

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Ethical Issues

This manuscript was approved in the ethics committee of Tabriz University of Medical Sciences. (IR.TBZMED.REC.1399.940).

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