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Comparative Outcomes of Etomidate versus Ketamine for Emergency Intubation in Septic Patients: A Randomized Controlled Trial

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ABSTRACT

Background: Etomidate and ketamine are extensively used for rapid sequence induction in septic patients, each with distinct hemodynamic and endocrine profiles. Etomidate preserves immediate cardiovascular stability but may cause adrenal suppression; ketamine provides sympathomimetic support but can induce hypotension in catecholamine-depleted states. Comparative evidence in sepsis-specific populations remains limited.

Methods: In this single-centre, randomised, single-blind controlled trial, 80 adult patients with sepsis requiring RSI in the emergency department were randomised to receive either etomidate (0.2–0.3 mg/kg IV) or ketamine (1–2 mg/kg IV) for induction. The primary outcome was 24-hour survival. Secondary outcomes included 7-day and 28-day survival, peri-intubation adverse events, vasopressor use within 24 hours, and corticosteroid administration. Data were analysed and interpretation was made.

Results: Baseline demographics, comorbidities, infection sources, and pre-intubation physiological parameters were comparable between groups. Survival at 24 hours (etomidate 92.5% vs. ketamine 95.0%, p=0.09), 7 days (87.5% vs. 87.5%, p=0.57), and 28 days (80.0% vs. 72.5%, p=0.09) did not differ suggestively. Peri-intubation cardiac arrest (2.5% each) and post-intubation hypotension (12.5% vs. 10.0%, p=0.84) rates were similar. However, vasopressor use within 24 hours was significantly higher with etomidate (45.0% vs. 17.5%, p<0.001), as was corticosteroid administration (15.0% vs. 5.0%, p=0.01).

Conclusion: The study has concluded that the use of neuromuscular blocking agents was higher in the ketamine group. Post-intubation physiological parameters, such as systolic blood pressure and pulse rate, were comparable, although oxygen saturation showed a statistically significant difference.

Key-words: Sepsis, Rapid sequence intubation, Etomidate, Ketamine, Adrenal suppression, Emergency airway management

INTRODUCTION

Sepsis remains a leading cause of serious illness and in-hospital death worldwide, and rapid, decisive airway management is frequently lifesaving for patients with severe infection and respiratory failure.

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Emergency endotracheal intubation in septic patients is high risk: these patients frequently have haemodynamic instability, deranged physiology and limited physiologic reserve, which increases the chance of peri-intubation difficulties such as severe hypotension, cardiac arrest and worsened organ dysfunction [1]. Choosing an induction agent that provides adequate sedation and facilitates intubation while minimising cardiovascular compromise and downstream adverse effects is therefore a central apprehension for clinicians performing rapid sequence induction in sepsis.

Etomidate and ketamine are two frequently used induction agents in emergency and critical care settings

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because both have relatively favourable immediate haemodynamic profiles compared with agents such as propofol. Etomidate is prized for maintaining blood pressure and heart rate at induction, thanks to minimal direct cardiac depression; its pharmacokinetic properties make it practical for single-dose use during RSI [2]. However, etomidate inhibits adrenal steroidogenesis by blocking 11β-hydroxylase; even a single bolus has been shown to produce transient adrenocortical suppression, and observational studies have raised apprehensions that this pharmacologic "adrenalectomy" could translate into worse outcomes in patients with sepsis who depend on endogenous corticosteroid responses to physiologic stress. Ketamine, a dissociative anaesthetic with sympathomimetic effects, offers the theoretical advantage of supporting blood pressure by increasing catecholamine release and sympathetic tone, making it attractive for hypotensive or catecholamine-dependent patients [3]. It also confers analgesia and preserves airway reflexes. Until now, ketamine's haemodynamic effects are complex: in patients with prolonged shock and depleted catecholamine reserves, ketamine can produce myocardial depression and hypotension, and some observational data report more frequent post-intubation hypotension compared with etomidate. Thus, the relative haemodynamic safety of ketamine vs etomidate in the heterogeneous population of septic patients is not entirely settled [4].

Randomised trials and meta-analyses to date have produced mixed signals. Initial randomised work and several single-centre studies suggested similar short-term outcomes between the two agents, but raised consistent findings of higher biochemical or clinical adrenal suppression after etomidate. A notable multicentre randomised trial and several subsequent randomised and observational studies have examined mortality, post-intubation hypotension and vasopressor requirements. While many studies showed no clear difference in long-term mortality, some reported increased vasopressor use or higher odds of adrenal insufficiency after etomidate [5]. Recent pooled Bayesian meta-analyses incorporating randomised trials and propensity-matched cohorts suggest a moderate probability that ketamine may be associated with a reduced risk of death compared with etomidate. However, credible intervals often cross unity and heterogeneity between studies limits definitive conclusions [5,6].

Against this uncertain background, clinicians face a practical dilemma when intubating septic patients: favour etomidate for perceived immediate haemodynamic stability at the potential cost of adrenal suppression, or favour ketamine for its sympathomimetic properties and possible endurance benefit, but with apprehension for peri-intubation hypotension in catecholamine-exhausted patients [6]. Existing randomised data specifically in septic populations are limited in size and scope; numerous trials pooled mixed critically ill cohorts, and observational studies are vulnerable to confounding by indication. Thus, an adequately powered randomised controlled trial focused on septic patients is needed to clarify whether a single induction dose of etomidate or ketamine leads to superior clinical results, including initial survival, vasopressor requirements, post-intubation hypotension and measures of organ dysfunction [7].

Therefore, the present randomised controlled trial was designed to directly compare etomidate and ketamine for single-dose induction in adult patients with sepsis requiring emergency intubation in the emergency department, with the primary aim of determining differences in early survival and important peri-intubation difficulties. By focusing on a clinically homogenous septic population and collecting detailed peri-procedural haemodynamic and adrenal function data, this study seeks to provide pragmatic evidence to inform induction-agent selection during one of the highest-risk interventions in septic care.

MATERIALS AND METHODS

Research Design- This study was conducted as a single-centre, randomised, single-blind, controlled trial with a 1:1 allocation ratio. The study was carried out over 12 months at our medical college hospital. Approval for the study was obtained from the Institutional Ethics Committee of our medical college. Due to the emergent and life-threatening nature of septic presentations requiring immediate airway involvement, written informed consent was delayed until the patient was stabilised. Consent was then obtained either from the patient or from an officially authorised representative as soon as possible. A total of 80 adult patients meeting the eligibility criteria were enrolled.

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Patients were randomised in a 1:1 ratio to receive either etomidate or ketamine as the induction agent. The randomisation sequence was computer-generated using variable block sizes and prepared by an independent statistician not involved in patient recruitment or clinical care. Allocation concealment was maintained via sequentially numbered, opaque, sealed envelopes. The treating physician preparing the study drug was aware of the assignment; however, the incubator and result assessors were blinded to the induction agent used. Etomidate group: received 0.2–0.3 mg/kg intravenous bolus of etomidate. Ketamine group: received 1–2 mg/kg intravenous bolus of ketamine. In both groups, rapid sequence intubation was performed using a standard protocol, with succinylcholine as the neuromuscular blocking agent unless contraindicated. Direct laryngoscopy or video laryngoscopy was used at the discretion of the incubator. Correct tube placement was confirmed clinically and by waveform capnography. All patients received standard sepsis management following the Surviving Sepsis Campaign guidelines, including oxygen supplementation or mechanical ventilation, timely intravenous antibiotics, and haemodynamic support as indicated.

Inclusion Criteria

- Age ≥ 18 years.
- Presentation to the ED with suspected or confirmed sepsis, as defined by the Third International Consensus Definitions for Sepsis and Septic Shock.
- Clinical requirement for rapid sequence induction and emergency endotracheal intubation.

Exclusion Criteria

- Cardiac arrest before intubation.
- Existing “Do Not Resuscitate” orders.
- Known or suspected adrenal insufficiency.
- Severe uncontrolled hypertension.
- Suspected or confirmed raised intracranial pressure.

Statistical Analysis- All analyses were performed on an intention-to-treat basis. Continuous variables were summarised as mean±standard deviation if normally distributed, or median with interquartile range for skewed data. Categorical variables were expressed as counts and percentages. Between-group comparisons for continuous variables were performed using Student’s *t*-test or the Mann–Whitney *U* test as appropriate. Categorical variables were compared using the Chi-square test or Fisher’s exact test. Risk differences and 95% confidence intervals were calculated for binary outcomes. A p-value < 0.05 was considered significant. Data analysis was performed using SPSS-27.

RESULTS

The mean age was somewhat higher in the etomidate group (73.0±12.8 years) compared to the ketamine group (71.0±14.3 years), with a similar male predominance (~59%). Comorbidities such as hypertension and diabetes mellitus were common, with hypertension present in 60% overall and diabetes in 41.3% of patients. Stroke was more frequent in the etomidate group (32.5% vs 20.0%), while COPD/asthma prevalence was somewhat higher in the etomidate group as well. Acute respiratory failure and pneumonia were the most common indications for intubation in both groups. The primary source of infection was the respiratory tract, with smaller contributions from intra-abdominal, skin/soft tissue, and urinary tract sources. Pre-intubation physiological parameters, including systolic blood pressure, pulse rate, oxygen saturation, qSOFA score, and SOFA change, were similar between groups. Serum lactate levels and pre-randomisation resuscitation were also comparable, signifying balanced hemodynamic and metabolic status before drug administration (Table 1).

Table 1: Baseline characteristics of septic patients undergoing emergency intubation

Characteristics	All patients (N=80) n (%)	Etomidate (N=40) n (%)	Ketamine (N=40) n (%)
Male gender	47 (58.8)	24 (60.0)	23 (57.5)
Age, mean±SD (years)	71.9±13.9	73.2±12.6	70.5±14.9
Comorbid disease			
Diabetes mellitus	33 (41.3)	15 (37.5)	18 (45.0)
Hypertension	48 (60.0)	25 (62.5)	23 (57.5)

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Stroke	21 (26.3)	13 (32.5)	8 (20.0)
Chronic kidney disease	10 (12.5)	5 (12.5)	5 (12.5)
COPD/asthma	6 (7.5)	4 (10.0)	2 (5.0)
Reasons for emergency intubation			
Acute respiratory failure	33 (41.3)	17 (42.5)	16 (40.0)
Pneumonia	30 (37.5)	14 (35.0)	16 (40.0)
Coma	13 (16.3)	7 (17.5)	6 (15.0)
Shock	2 (2.5)	1 (2.5)	1 (2.5)
Other	2 (2.5)	1 (2.5)	1 (2.5)
Sources of infection			
Respiratory tract	58 (72.5)	29 (72.5)	29 (72.5)
Intra-abdominal	7 (8.8)	4 (10.0)	3 (7.5)
Skin or soft tissue	5 (6.3)	2 (5.0)	3 (7.5)
Urinary tract	4 (5.0)	2 (5.0)	2 (5.0)
Glasgow Coma Scale before intubation			
14–15	28 (35.0)	13 (32.5)	15 (37.5)
9–13	26 (32.5)	15 (37.5)	11 (27.5)
3–8	26 (32.5)	12 (30.0)	14 (35.0)
Physiological parameters before intubation			
Systolic BP, mean±SD (mmHg)	115.5±31.7	112.9±30.7	118.1±32.5
Pulse rate, mean±SD (bpm)	107.2±24.9	108.8±24.5	105.6±25.2
Oxygen saturation, median (IQR) (%)	92 (83–98)	92 (84–98)	92 (83–98)
qSOFA score, mean±SD	2.2±0.4	2.2±0.4	2.1±0.3
Delta SOFA score at ED, mean±SD	4.8±1.9	4.6±1.9	4.9±1.9
Initial serum lactate, median (IQR)(mmol/L)	3.3 (2.4–6.5)	3.6 (2.4–7.6)	3.2 (2.2–5.4)
Treatment before randomisation			
Received IV antibiotic	66 (82.5)	33 (82.5)	33 (82.5)
IV fluid volume, median (IQR) (mL)	1000 (600–1500)	1000 (500–1500)	1200 (650–1500)

Median attempts required for intubation were identical (1 [IQR 1–1]) in both groups, with similar first-attempt success rates (90.0% vs. 87.5%, p=0.846). Failed intubation was rare, occurring in only one patient in the etomidate group and none in the ketamine group. Indicators of difficult intubation were infrequent overall, though a higher proportion of large tongue cases was observed in the ketamine group (5.0% vs. 0.8%), approaching statistical significance (p=0.066). Use of neuromuscular blocking agents was suggestively more common in the ketamine group (77.5% vs. 65.0%, p=0.040). Glottis exposure grades were broadly similar between groups, with grade I visualisation being the most frequent finding in both. Post-intubation physiological parameters, including systolic blood pressure and pulse rate, were not significantly different, though oxygen saturation differences reached statistical significance (p=0.021), with both groups achieving a median of 100% (Table 2).

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Table 2: Intubation conditions of septic patients undergoing emergency intubation

Variable	Etomidate (N=40) n (%)	Ketamine (N=40) n (%)	p-value
Total number of attempts, median	1 (1–1)	1 (1–1)	0.57
Successful in the first attempt	36 (90.0)	35 (87.5)	0.84
Failed intubation	1 (2.5)	0	0.49
Difficult intubation indicators			
Large tongue	0 (0.8)	2 (5.0)	0.06
Limited mouth opening	0 (0.8)	0 (0.8)	1
Short hypo-mental distance	1 (2.5)	1 (2.5)	1
Short thyro-hyoid distance	1 (2.5)	2 (5.0)	0.44
Poor neck mobility	0 (0.8)	1 (2.5)	1
Pretreatment with intravenous fluid	13 (32.5)	12 (30.0)	0.89
Neuromuscular blocking agent used	26 (65.0)	31 (77.5)	0.04
Glottis exposure grade	-	-	0.34
I = Entire vocal cord visible	21 (52.5)	25 (62.5)	-
II = Part of the vocal cord visible	16 (40.0)	13 (32.5)	-
III = Epiglottis only visible	3 (7.5)	2 (5.0)	-
IV = Epiglottis not visualised	0	0	
Physiological parameters after intubation			
Systolic BP, mean±SD (mmHg)	132.9±46.9	142.6±37.9	0.06
Pulse rate, mean±SD (bpm)	116.6±23.5	112.5±21.5	0.13
Oxygen saturation, median (IQR) (%)	100 (100–100)	100 (100–100)	0.02

Among septic patients undergoing emergency intubation, short-term survival at 24 hours was high in both groups (92.5% with etomidate vs. 95.0% with ketamine), with no statistically significant difference (p=0.09). Survival rates at 7 days were identical (87.5% each), while 28-day survival rates curved higher in the etomidate group (80% vs. 72.5%) but without statistical significance (p=0.09). Adverse events during the peri-intubation period were infrequent and similar between groups. Cardiac arrest occurred in 2.5% of patients in each group, and failed intubation was rare. Post-intubation hypotension occurred in roughly one in ten patients in both arms. Fluid administration volumes in the first three hours post-intubation were similar between groups. Particularly, vasopressor requirement within the first 24 hours after intubation was suggestively higher in the etomidate group (45% vs. 17.5%, p<0.001), suggesting a greater tendency toward hemodynamic support following etomidate use. In addition, corticosteroid administration was more frequent in the etomidate group (15% vs. 5.0%, p=0.01), potentially reflecting clinician response to adrenal suppression risk (Table 3).

Table 3: Survival outcomes and peri-intubation adverse events in septic patients undergoing emergency intubation

Outcome	Etomidate (N=40) n (%)	Ketamine (N=40) n (%)	Risk Difference (95% CI) %	p-value
Survival outcomes				
24-h survival	37 (92.5)	38 (95.0)	2.5 (−6.4, 11.4)	0.09
7-day survival	35 (87.5)	35 (87.5)	0 (−12.2, 12.2)	0.57
28-day survival	32 (80.0)	29 (72.5)	7.5 (−7.8, 22.8)	0.09
Peri-intubation adverse events				
Cardiac arrest	1 (2.5)	1 (2.5)	0 (−6.1, 6.1)	1

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Failed intubation	1 (2.5)	0	2.5 (−2.4, 7.4)	0.15
Post-intubation hypotension	5 (12.5)	4 (10.0)	2.5 (−9.1, 14.1)	0.84
Total fluid in first 3 h, median (IQR), mL	1000 (600–1500)	1000(600–1500)	0 (−154, 123)	0.82
Vasopressor use within 24 h after intubation	18 (45.0)	7 (17.5)	27.5 (10.0, 45.0)	<0.001
Intravenous corticosteroid use	6 (15.0)	2 (5.0)	10.0 (0.3, 19.7)	0.01

DISCUSSION

In this randomised controlled trial comparing single-dose induction with etomidate versus ketamine in septic patients undergoing emergency intubation, the principal result was that early (24-, 7-, and 28-day) survival did not differ significantly between groups. However, etomidate was associated with a notably higher rate of vasopressor use within 24 hours post-intubation. These results add both clarity and gradation to an ongoing and often conflicting body of evidence regarding optimal induction agents in septic patients.

First, our survival results are parallel with several prior reports. The large multicentre RCT by Jabre et al. comparing etomidate versus ketamine in critically ill patients established no significant difference in organ dysfunction and implied comparable outcomes between agents [1]. Similarly, a modern RCT examining SOFA scores and 30-day mortality found no significant differences between the two agents [8]. Moreover, our trial's survival data echo those observations, suggesting that in sepsis, at least, short-term mortality may not hinge critically on the choice of induction agent.

Equally, the important increase in vasopressor use after etomidate in our cohort raises important clinical considerations. Etomidate's well-described adrenal suppression, via reversible inhibition of 11-β-hydroxylase, is of relevance in septic shock, where endogenous cortisol is vital to maintaining vascular tone and responsiveness to vasopressors [2]. Observational studies and registry data have underscored this risk: one NEAR cohort analysis found that ketamine use in sepsis was associated with nearly triple the odds of post-procedure hypotension compared with etomidate [9]. Particularly, that study focused on immediate peri-intubation hypotension, not on post-intubation vasopressor needs, a somewhat different but related outcome. Our results complement those findings by signifying that etomidate may cause more delayed hemodynamic instability requiring vasopressors, even though immediate hypotension may be less frequent.

Systematic reviews and meta-analyses further illuminate this dynamic. A recent meta-analysis comprising RCTs found that although mortality and post-intubation hypotension rates were comparable between etomidate and ketamine, adrenal insufficiency was suggestively more common after etomidate [7]. Another systematic review and meta-analysis of 14 RCTs and controlled studies similarly found no survival difference. Still, they reported that ketamine was associated with increased vasopressor use, while etomidate had higher adrenal insufficiency rates [10]. These tendencies mirror our own: while survival may not differ, etomidate's physiological impact appears to translate into greater hemodynamic support needs after intubation.

Our results also task the prevailing assumption that ketamine offers superior hemodynamic stability. The NEAR cohort experienced more immediate hypotension after ketamine in septic patients [11], and a meta-analysis confirmed etomidate had a lower risk of post-induction hypotension compared to ketamine [12]. However, in catecholamine-depleted septic shock, ketamine's indirect sympathomimetic effects may be rounded, rendering its hemodynamic profile less favourable

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than expected [13]. In contrast, our results suggest that etomidate's adverse downstream effect, hormonal suppression, may manifest as increased vasopressor requirement, even if blood pressure is initially better preserved.

CLINICAL IMPLICATIONS

Clinicians choosing an induction agent in sepsis face a trade-off: etomidate may preserve immediate blood pressure but risks adrenal suppression; ketamine may lower initial adrenal insult yet potentially predispose to peri-intubation hypotension, especially in catecholamine-exhausted patients. Our data suggest that while neither agent offers a death edge, the choice influences post-intubation hemodynamic management.

LIMITATIONS

This trial has limitations: it was single-centred, which may limit generalizability. Though randomised, whether the results apply to patients with distinct subtypes of sepsis remains to be tested. We did not measure cortisol levels or directly confirm adrenal suppression, so we infer mechanisms indirectly and rely on prior physiologic literature.

CONCLUSIONS

The study comparing etomidate and ketamine for emergency intubation in septic patients found no significant differences in intubation attempts or first-pass success rates. Intubation conditions were comparable, with minor variations in glottic exposure and difficult intubation indicators. Use of neuromuscular blocking agents was higher with ketamine. Post-intubation physiological parameters, including systolic blood pressure and pulse rate, were similar, though oxygen saturation showed a statistically significant difference. Etomidate was associated with higher vasopressor requirements and increased corticosteroid use within 24 hours, consistent with adrenal suppression. Immediate peri-intubation adverse events were infrequent and comparable across groups. These findings suggest that while both agents provide similar conditions for intubation, the downstream hemodynamic and endocrine effects of etomidate warrant caution. Drug choice should be individualised, balancing risks of adrenal suppression with potential hypotension in catecholamine-depleted patients. Larger multicentre trials assessing adrenal function and long-term outcomes are needed to guide optimal induction in sepsis.

Future studies should evaluate adrenal biomarkers after etomidate in sepsis and test if corticosteroid supplementation alters outcomes. Trials may also explore ketamine induction with vasopressor prophylaxis or adjuvants to combine benefits of both drugs.

CONTRIBUTION OF AUTHORS

Research concept- Chetan Goyal, Deepa Agarwal
Research design- Chetan Goyal
Supervision- Deepa Agarwal
Materials- Deepa Agarwal
Data collection- Chetan Goyal
Data analysis and interpretation- Chetan Goyal, Deepa Agarwal
Literature search- Chetan Goyal, Deepa Agarwal
Writing article- Deepa Agarwal
Critical review- Chetan Goyal, Deepa Agarwal
Article editing- Chetan Goyal
Final approval- Chetan Goyal, Deepa Agarwal

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