Clinical outcomes after single induction dose of etomidate versus ketamine for emergency department sepsis intubation: a randomized controlled trial

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Abstract

Background: Patients with sepsis often require emergency intubation. In emergency departments (EDs), rapid-sequence intubation with a single-dose induction agent is standard practice but the best choice of induction agent in sepsis remains controversy. High quality RCTs are needed to determine the optimal induction agents in sepsis.

Methods: We conducted a randomized, controlled, single-blind trial in the ED. We included septic patients who were aged at least 18 years and required sedation for emergency intubation. Patients were randomly assigned by a blocked randomization to receive 0.2-0.3 mg/kg of etomidate or 1-2 mg/kg of ketamine for intubation. Outcomes were compared with intention-to-treat analysis. The primary objective was to compare the 28-day survival outcomes between etomidate and ketamine. The secondary objectives outcomes were to compare 24-hour and 7-day survival rates, and adverse events after intubation.

Results: 260 septic patients were enrolled; 130 patients/ drug arm whose baseline characteristics were well balance at baseline. In the etomidate group, 105 patients (80.8%) were alive at 28 days, as compared with 95 patients (73.1%) in the ketamine group (risk difference [RD], 7.7%; 95% confidence interval [CI], -2.5% to 17.9%; P=0.092). There was no significant difference in the proportion of patients who survived at 24 hours (91.5% vs. 96.2%; P=0.097) and survived at 7 days (87.7% vs. 87.7%; P=0.574). A significantly higher proportion of the etomidate group needed a vasopressor within 24 hours after intubation: 43.9% vs. 17.7%, RD, 26.2% (95% CI, 15.4% to 36.9%; P<0.001).

Conclusions: In patients with sepsis who needed emergency intubation in the ED, there were no differences in early and late survival rates between etomidate and ketamine. However, etomidate associated with higher risks of early vasopressor needed after intubation.

Trial registration: The trial protocol was registered in Thai Clinical Trials Registry (identification number; TCTR20210213001). Registered 13 February 2021 – Retrospectively registered, https://www.thaiclinicaltrials.org/export/pdf/TCTR20210213001.

Background

Sepsis is a major medical emergency that is often seen in emergency departments (ED). With a high rate of morbidity and mortality, treatment and resuscitation should begin immediately[1]. The incidence of sepsis-induced hypoxemic respiratory failure in the United States is approximately 6–7%[2, 3]. These patients often require emergency orotracheal intubation along with mechanical ventilator to optimize their oxygenation and ventilation[1, 4]. Rapid sequence intubation (RSI) with the administration of an induction and a paralytic agent is considered the method of choice in the ED. However, the best induction agent for emergency intubation in the sepsis remains controversy.

Etomidate is a nonbarbiturate hypnotic that is most often used in RSI[5]. It has a short duration of action and causes little cardiovascular depression[6]. Single-dose etomidate can inhibit adrenal mitochondrial

11-β-hydroxylase activity and may induce reversible adrenal insufficiency (AI)[7]. Reversible AI may also be exacerbated in patients with critical illness-related corticosteroid insufficiency, particularly in sepsis and septic shock[8]. However, the clinical significance of this association is unclear. Previous meta-analysis, comparing etomidate and alternative induction agents, concluded that etomidate was associated with higher rates of mortality in patients with sepsis[9], but more recent studies have reported conflicting results[10, 11].

Ketamine is an alternative induction agent in sepsis. It increases blood pressure and heart rate through catecholamine release and is considered a safe and valuable alternative to etomidate for emergency intubation in patients with sepsis[12]. However, several studies suggest that ketamine may be associated with a greater risk of hypotension compared to etomidate, especially in patients with catecholamine depletion[5, 11, 13]. Furthermore, there is a concern that ketamine may be related to increased myocardial ischemia, especially in elderly patients[14].

There is no consensus on which induction agent is be preferred for emergency intubation in sepsis. The recent meta-analysis of two small randomized controlled trials (RCTs) and 16 observational studies suggested that single-dose etomidate, compared to alternative induction agents, was not associated with increased mortality in patients with sepsis. However, the finding might subject to bias and confounding[11]. High quality RCTs are needed to determine the optimal induction agents in sepsis. We, therefore, conducted a RCT that aimed to compare the survival outcomes, early haemodynamic outcomes, and peri-intubation adverse events after single-dose induction between etomidate and ketamine.

Methods

Trial design and oversight

From March 2019 to December 2020, this single-centered, randomized, single-blind, controlled trial, with 1:1 allocation, was conducted by the Emergency medicine research group in Thammasat University Hospital (TUH) in Pathum Thani, Thailand. TUH is an 800-bed tertiary academic teaching hospital in the suburbs north of Bangkok, with approximately 1.1 million people living in the area. The ED of TUH sees 60,000 patients annually and about 500 patients need emergency intubation each year. A previous study showed very high success rate of emergency intubation overall and at the first attempt rate in the ED of TUH (99.4% and 74.7%, respectively)[15].

Patient population

Patients with suspected sepsis who were 18 years or older and who needed an induction agent for emergency intubation in the ED were eligible for inclusion. Exclusion criteria were: (1) cardiac arrest before intubation, (2) patient with a do-not-resuscitate order, (3) known or suspected to have adrenal insufficiency, (4) severe hypertension (blood pressure before randomization over 180/110 mmHg), and

(5) suspected or evidenced of increased intracranial pressure. There is no exclusions after randomization criteria in the trial.

Randomization and treatment

Patients were randomly assigned to receive a single-dose induction agent either etomidate (Lipuro, B. Braun Melsungen, Germany) administered as a 0.2–0.3 mg/kg intravenous bolus, or to ketamine (Ketalar, PAR Pharmaceutical, Ireland) administered as a 1–2 mg/kg intravenous bolus. The randomization sequence was determined using a computer-generated randomization table with a block size of four, by a statistician who was not involved in determining patient eligibility, drug administration, intubating procedure, or outcomes assessment. The drug allocation sequence was kept inaccessible to the research team throughout the study period. Patient assignment was placed into sequentially numbered sealed opaque envelops. The emergency physician enrolling patients was responsible for opening these envelops and preparing the study agent, but was not involved in intubation process. None of the emergency physicians enrolling patients were members of the staff in the in-patient ward, and they had no influence on the management of the patients after they were admitted into hospital.

All patients received the same standard RSI protocol, except for the single-dose induction agent. The use of a neuromuscular blocking agent immediately after induction (succinylcholine as a 1.5 mg/kg intravenous bolus) depended on the clinical state of the patient and the presence of any contraindications. Patients were intubated by either the direct laryngoscopy technique (Macintosh) or video laryngoscopy technique (GlideScope). Intratracheal tube positioning was confirmed by clinical assessments and capnometers with capnographs.

The definition of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock[16]. Patients in both groups received same standard therapy in accordance with International Surviving Sepsis Campaign guidelines[17], including respiratory support, fluid resuscitation, early antimicrobials, macro- and micro-circulation management.

Outcomes

The primary outcome was the 28-day survival. The secondary outcomes were the 24-hour survival, 7-day survival, early hemodynamic parameters after intubation, amount of fluid required in the first three hours, and occurrence of peri-intubation adverse events. Peri-intubation adverse events included: cardiac arrest (during or immediately after intubation), failed intubation, post-intubation hypotension (systolic blood pressure below 90 mmHg, or mean arterial blood pressure below 65 mmHg), and use of a vasopressor (norepinephrine, epinephrine, or dopamine) within the first 24 hours after intubation. Outcomes were assessed by trained research coordinators, who were unaware of treatment assignment.

Sample size estimation

A pilot study was done to obtain the preliminary data for the calculation of a sample size for the primary outcome. Our power was determined by the survival rate of the pilot population. We determined that a

group of 130 patients in etomidate allocation and a group of 130 patients in ketamine allocation were needed to detect the effect size with 80% power and type-I error of 0.05.

Statistical analysis

The independent data monitoring committee performed interim analysis every 6 months. We used the Haybittle-Peto boundary to determine the upper and lower stopping boundaries for the primary outcome, with no adjustment in the final analysis.

The survival outcomes were analyzed without adjustment in the intention-to-treat population, which included all the patients who been randomized. All included patients were confirmed to have received the assigned intervention. Trial data were summarized by the calculation of means and standard deviations for normally distributed variables, median and interquartile ranges for non-normally distributed variables, and frequency and percentage for categorical variables. The magnitude of the difference between two percentages was demonstrated by the risk difference with 95% confidence intervals. All statistical tests were two-sided. A p value less than 0.05 was considered to be statistically significance. All analyses were performed using STATA software version 14.0 (StataCorp, College Station, TX).

Results

Patients and interventions

Of 1,015 patients who underwent emergency intubation and were screened for eligibility, 272 (26.8%) were enrolled. Twelve patients were excluded because very high blood pressure before intubation (Fig. 1). The remained 260 patients with sepsis underwent randomization and were followed up for 28 days (130 patients in the etomidate group and 130 in the ketamine group). The primary outcome was obtained for all patients. The characteristics of patients were well balanced at baseline (Table 1). The physiological parameters before intubation were also similar in the two groups. The key predictors of mortality in sepsis (delta SOFA score and initial serum lactate) were also similar in the two groups.

Table 1
Characteristics of the patients at baseline.

Characteristic	Etomidate (N = 130) n (%)	Ketamine (N = 130) n (%)
Male gender	77 (59.2)	76 (58.5)
Age, mean (± SD) (years)	73.2 (± 12.6)	70.5 (± 14.9)
Comorbid disease	48 (36.9)	59 (45.4)
Diabetic mellitus	80 (61.5)	76 (58.5)
Hypertension	43 (33.1)	26 (20.0)
Stroke	17 (13.1)	14 (10.8)
Chronic kidney disease	12 (9.2)	8 (6.2)
COPD/asthma	55 (42.3)	52 (40.0)
Reasons for emergency intubation	46 (35.4)	50 (38.5)
Acute respiratory failure	23 (17.7)	19 (14.6)
Pneumonia	4 (3.1)	3 (2.3)
Coma	2 (1.5)	6 (4.6)
Shock	95 (73.1)	92 (70.8)
Other	12 (9.2)	12 (9.2)
Sources of infection	8 (6.2)	9 (6.9)
Respiratory tract	7 (5.4)	6 (4.6)
Intra-abdominal	8 (6.1)	11 (8.5)
Skin or soft tissue	42 (32.3)	51 (39.2)
Urinary tract	49 (37.7)	36 (27.7)
Other	39 (30.0)	43 (33.1)
Glasgow coma scale before intubation	112.9 (± 30.7)	118.1 (± 32.5)
14–15	108.8 (± 24.5)	105.6 (± 25.2)
9–13	92 (84, 98)	92 (83, 98)
3–8	2.2 (± 0.4)	2.1 (± 0.3)
Physiological parameters before intubation	4.6 (± 1.9)	4.9 (± 1.9)
Systolic blood pressure, mean (± SD) (mmHg)	3.6 (2.4, 7.6)	3.2 (2.2, 5.4)
Pulse rate, mean (± SD) (bpm)		

Characteristic	Etomidate (N = 130) n (%)	Ketamine (N = 130) n (%)
Oxygen saturation, median (IQR) (%)		
qSOFA score, mean (± SD)		
Delta SOFA score at ED, mean (± SD)		
Initial serum lactate, median (IQR) (mmol/L)		

Intubation conditions between the two groups were also similar (Table 2), including the total number of attempts, success at the first attempt, difficult intubation indicators, pretreatment with intravenous fluid, glottic exposure grade, and patients' physiological parameters after intubation. However, the proportion of patients who were received neuromuscular blocking agent during intubation was significantly higher (p = 0.04) in the ketamine group than in the etomidate group (76.9% vs. 64.6%, respectively).

Table 2
Intubation conditions of the study patients.

Intubation condition	Etomidate (N = 130) n (%)	Ketamine (N = 130) n (%)	P value
Total number of attempts, median (IQR)	1 (1, 1)	1 (1, 1)	0.579
Successful in the first attempt	116 (89.2)	114 (87.7)	0.846
Failed intubation	2 (1.5)	0	0.498
Difficult intubation indicator	1 (0.8)	7 (5.4)	0.066
Large tongue	1 (0.8)	1 (0.8)	1.000
Limited mouth opening	3 (2.3)	3 (2.3)	1.000
Short hypo-mental distance	2 (1.5)	5 (3.9)	0.447
Short thyro-hyoid distance	1 (0.8)	2 (1.5)	1.000
Poor neck mobility	42 (32.3)	40 (30.8)	0.894
Pretreatment with intravenous fluid	84 (64.6)	100 (76.9)	0.040
Neuromuscular blocking agent used			0.346
Glottis exposure grade			
I = Visualized entire vocal cord	68 (52.3)	80 (61.5)	0.068
II = Visualized part of vocal cord	51 (39.2)	41 (31.5)	0.139
III = Visualized epiglottis only	10 (7.7)	9 (6.9)	0.021
IV = non-visualized epiglottis	1 (0.8)	0	
Physiological parameters after intubation	132.9 (± 46.9)	142.6 (± 37.9)	
Systolic blood pressure,	116.6 (± 23.5)	112.5 (± 21.5)	
- mean (± SD) (mmHg)	100 (100, 100)	100 (100, 100)	
Pulse rate, mean (± SD) (bpm)			
Oxygen saturation,			
- median (IQR) (%)			

Primary and secondary outcomes

In the etomidate group, 105 patients (80.8%) were alive at 28th days compared to 95 patients (73.1%) in the ketamine group (risk difference [RD], 7.7%; 95% confidence interval [CI], -2.5–17.9%; P = 0.092). There were no significant differences between the etomidate group and the ketamine group in the proportion of

patients who survived at 24 hours (91.5% vs. 96.2%, respectively; RD, 4.7%; 95% CI, -1.2–10.4%; P = 0.097), and survival at 7 days (87.7% vs. 87.7%; RD, 0%; 95% CI, -7.9–7.9%; P = 0.574) (Table 3 and Fig. 2).

Table 3
Primary and secondary outcomes.

Outcome	Etomidate (N = 130) n (%)	Ketamine (N = 130) n (%)	Risk difference (95% confidence interval) (%)	P value
Survival outcomes	119 (91.5)	125 (96.2)	4.7 (-1.2, 10.4)	0.097
24-hour survival	114 (87.7)	114 (87.7)	0 (-7.9, 7.9)	0.574
7-day survival	105 (80.8)	95 (73.1)	7.7 (-2.5, 17.9)	0.092
28-day survival				
Peri-intubation adverse events	2 (1.5)	2 (1.5)	0 (-2.9, 2.9)	1.000
Cardiac arrest	2 (1.5)	0	1.5 (-0.6, 3.6)	0.155
Failed intubation	15 (11.5)	14 (10.8)	0.7 (-6.9, 8.4)	0.843
Post-intubation hypotension	1,000	1,000	0	0.827
Total fluid required in the first	(600, 1,500)	(600, 1,500)	(-153.9, 123.1)	< 0.001
three hours, median (IQR) ml	57 (43.9)	23 (17.7)	26.2 (15.4, 36.9)	
Used of a vasopressor medication				
within 24 hours after intubation				

Regarding peri-intubation adverse events, cardiac arrest during intubation occurred in two patients (1.5%) in the etomidate group and two patients (1.5%) in the ketamine group (RD, 0%; 95% CI, -2.9–2.9%; P = 1.0). Two patients (1.5%) in the etomidate group were diagnosed with failed intubation, but none in the ketamine group. There was no significant difference between the study groups in the proportion of patients with post-intubation hypotension (11.5% vs. 10.8%; RD, 0.7%; 95% CI, -6.9–8.4%; P = 0.843); however, there was a significant difference between the etomidate group and the ketamine group in the proportion of patients who needed a vasopressor within 24 hours after intubation (43.9% vs. 17.7%, respectively; RD, 26.2%; 95% CI, 15.4–36.9%; P < 0.001) (Table 3 and Fig. 2).

Discussion

The main goal of this study were to compare the clinical outcomes between the two induction agents that most commonly used for emergency intubation in EDs. We found no significant differences in survival at 24-hour, 7-day, and 28-day in sepsis patients intubated with using etomidate or ketamine. We also found no significant difference in patients' physiological parameters after intubation, and peri-intubation adverse events, including: (1) peri-intubation cardiac arrest, (2) failed intubation, and (3) post-intubation hypotension. However, more patients who received single-dose etomidate required a vasopressor within 24 hours after intubation.

There is still controversy regarding the safety of single-dose etomidate as an induction agent for emergency intubation in patients with sepsis. Several RCTs compared mortality outcomes between etomidate and alternative induction agents[12, 18–20] but most of them included a broad range of critically ill patients or trauma cases; patients with sepsis were only a subgroup of population (15–50%) or were in a secondary analysis. One RCT conducted by Tekwani at el (2010) studied patients with suspected sepsis who were intubated in the ED[21], which focused mainly on the length of hospital stay and not patients' clinical outcomes. Our study was designed to answer this specific controversy by including only patients with suspected sepsis who presented to the ED and showed that single-dose etomidate was an acceptable choice in patients with sepsis in the ED.

Etomidate can suppress the adrenal synthesis of cortisol by inhibiting 11-β hydroxylase, the enzyme responsible for the conversion 11-deoxycortisol to cortisol[7] as a result adrenal function may be blunted for 4–24 hours after a single dose but inhibition can last up to 72 hours[22, 23]. Relative AI means a lack of adrenocortical reserve and has also been found in patients with septic shock. Therefore, single-dose etomidate for emergency intubation should be used with caution as it may worsen patient outcomes[22]. A previous meta-analysis from Chan et al (2012) concluded that using etomidate for RSI was associated with higher rates of AI and 28-day mortality in patients with sepsis[9]. By contrast, a more recent meta-analysis from Gu et al (2015) indicates that although single-dose etomidate increased the risk of AI, it was not associated with increased overall mortality in patients with sepsis[10]. Our findings support this recent meta-analysis by showing that single-dose etomidate was not associated with a significantly increased risk of mortality in patients with suspected sepsis in the ED.

Previous studies comparing etomidate and ketamine in acutely ill patients showed that there were no differences in major peri-intubation adverse events, including peri-intubation cardiac arrest, change in blood pressure after intubation, and the total volume of intravenous fluid needed after intubation[12, 20]. Our study supports these findings. However, there is a controversy surrounding post-intubation hypotension. Single-dose induction agents can impact patients' haemodynamic status, especially in critical ill patients who need emergency intubation. Although both etomidate and ketamine are considered heamodynamically stable induction agents, there remain concerns that they might cause post-intubation hypotension, particular in patients with sepsis[5, 9, 11, 24–26]. Multi-center observational studies report that ketamine is associated with higher risks of post-intubation hypotension after emergency intubation compared to alternative agents[5], including etomidate[11, 26]. These findings are

supported by Smischney et al (2020), who studied critically ill patients in 16 ICUs, and found less post-intubation hypotension with etomidate compared to alternative agents[24]. However, a multi-center observational study in ED reported a lower risks of post-intubation hypotension in heamodynamically unstable patients when using ketamine compared to midazolam or propofol[25]. In the emergency department, post-intubation hypotension might be associated with a higher risk of mortality[27, 28].

Limitation

Our study was limited by its sample size and although our results show no difference in patients' physiological parameters and post-intubation hypotension after a single-dose etomidate or ketamine, we had limited statistical power. Moreover, we did not calculate the sample size to demonstrate the differences in physiologic parameters in the design phase of the trial. However, our study has provided prospectively collected data on 28-day mortality rates that could be used for future high-quality and adequately powered studies comparing the immediate effects of etomidate and ketamine as well as mortality.

Conclusion

In patients with clinically suspected sepsis who needed emergency intubation in ED, there was no difference in early and 28-day survival rates between etomidate and ketamine. However, etomidate was associated with higher risks of early vasopressor use after intubation.

Abbreviations

ED
Emergency department
RSI
Rapid sequence intubation
AI
Adrenal insufficiency
RD
Risk difference
RCT
Randomized controlled trial
ICU
Intensive care unit

Declarations

Ethics approval and consent to participate

The trial was approved by the Human Research Ethics Committee of the Faculty of Medicine of Thammasat University. Because of the sudden and life-threatening nature of patients who needed emergency intubation, the process of obtaining written informed consent was deferred until after the emergency had passed. We sought written informed consent to continue data collection after intubation from the patient or, if the patient was unable to give consent, a legal representative.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there have no competing interests.

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Authors' contributions

Conceptualization: WS, AB, KA. Protocol development: WS, KA. Data collection: AB, KD, CL, KA, II, ND, ID, YS, TU, CP. Data analysis: WS, AB. Writing and editing manuscript: WS, VP. All authors read and approved the final manuscript.

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Figures

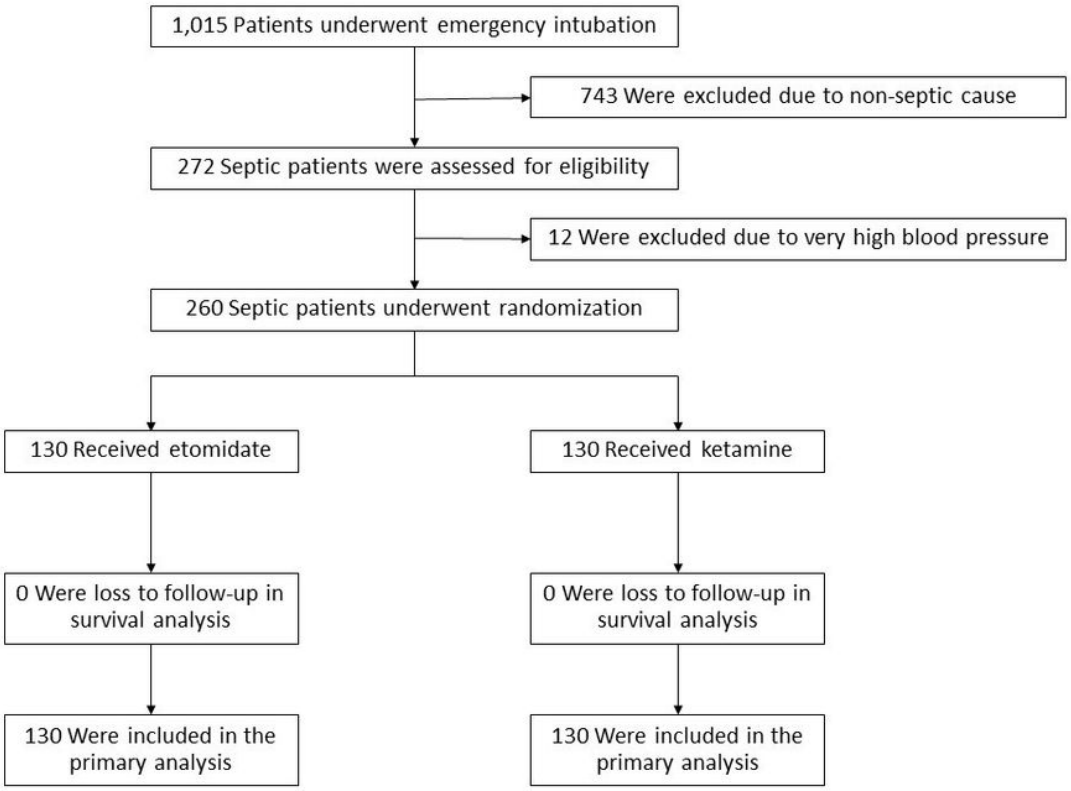

Figure 1

Flow diagram of the study patients enrolled.

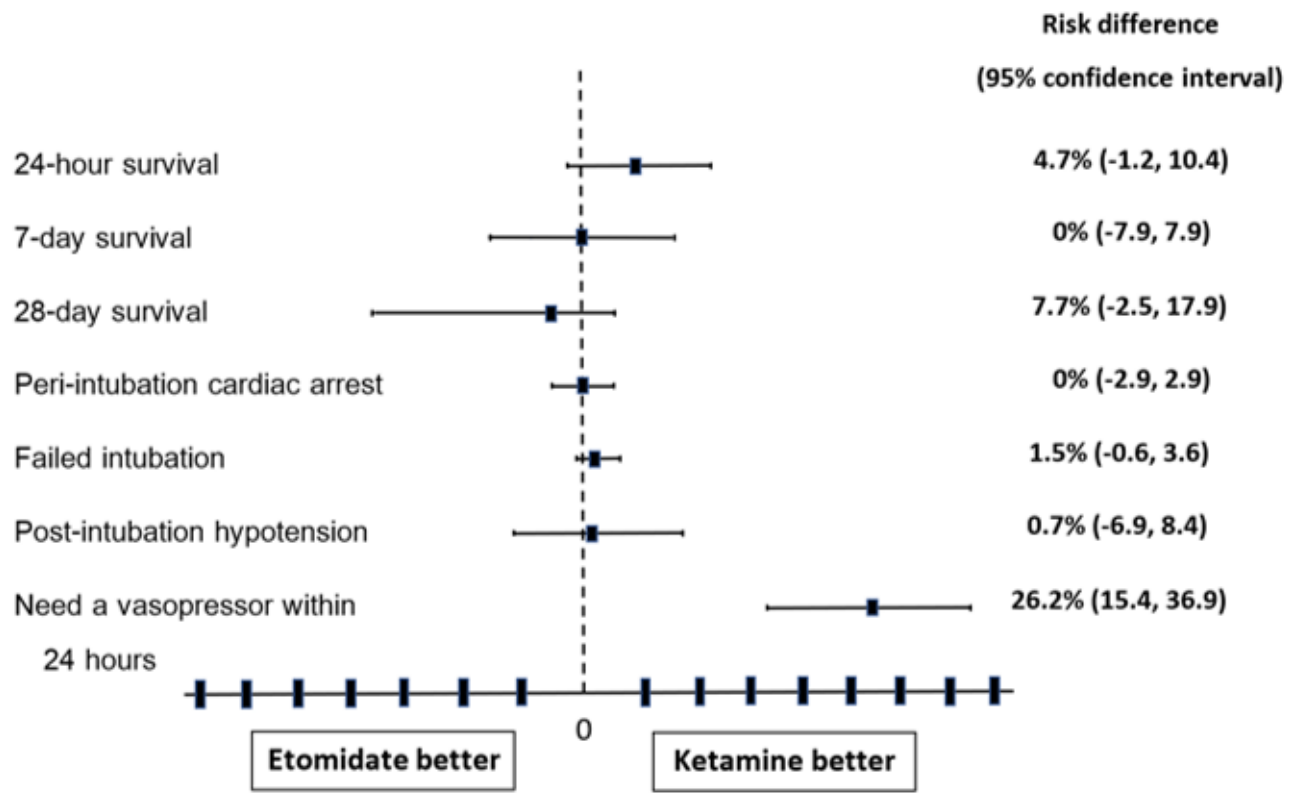

Figure 2

Primary and secondary outcomes.