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Original Contributions

THE EFFECT OF KETAMINE VERSUS ETOMIDATE FOR RAPID SEQUENCE INTUBATION ON MAXIMUM SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE: A RANDOMIZED CLINICAL TRIAL

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□ **Abstract—Background: The use of induction agents for rapid sequence intubation (RSI) has been associated with hypotension in critically ill patients. Choice of induction agent may be important and the most commonly used agents are etomidate and ketamine. Objective: This study aimed to compare the effects of a single dose of ketamine vs. etomidate for RSI on maximum Sequential Organ Failure Assessment (SOFA) score and incidence of hypotension. Methods: This single-center, randomized, parallel-group trial compared the use of ketamine and etomidate for RSI in critically ill adult patients in the emergency department. The study was performed under Exception from Informed Consent. The primary outcome was the maximum SOFA score within 3 days of hospitalization. Results: A total of 143 patients were enrolled in the trial, 70 in the ketamine group and 73 in the etomidate group. Maximum median SOFA score for the ketamine group was 6.5 (interquartile range [IQR] 5–9) vs. 7 (IQR 5–9) for etomidate with no significant difference (–0.2; 95% CI –1.4 to 1.1; $p = 0.79$). The incidence of post-intubation hypotension was 28% in the ketamine group vs. 26% in the etomidate group (difference 2%; 95% CI –13% to 17%). There were no significant differences in intensive care unit outcomes. Thirty-day mortality rate for the ketamine group was 11% (8 deaths) and for the etomidate group was 21% (15 deaths), which was not statistically different. Conclusions: There were no significant differences in maximum SOFA score or post-intubation hypotension between critically ill adults receiving ketamine vs. etomidate for RSI.**

□ **Keywords—rapid sequence intubation; sedation; ketamine; etomidate**

INTRODUCTION

Rapid sequence intubation (RSI) is the most common technique used in emergency tracheal intubation and is defined as the administration of an induction agent and a neuromuscular blocking agent in quick succession (1). RSI increases first-attempt success without increasing risk for complications (2). However, the use of induction agents has been associated with the risk of hypotension and hemodynamic compromise in critically ill patients (3). Choice of induction agent may be important and the most commonly used induction agents are etomidate and ketamine (4).

Etomidate is the most commonly used induction agent for RSI in the emergency department (ED), in large part due to its rapid onset, short duration, and low risk of hemodynamic effect and hypotension (1,5,6). There have been safety concerns raised in patients with sepsis due to its potential risk of adrenal suppression secondary to transient inhibition of 11-β-hydroxylase based on obser-

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vational data (7–15). However, subsequent data suggest little impact on long-term outcomes, even in patients with sepsis (16–26).

Ketamine, a dissociative anesthetic, has been available for human use since the 1970s, but has expanded in use recently as an alternative induction agent due to its stable hemodynamic profile and lack of adrenal suppression (27–31). It has been suggested that ketamine may have a positive hemodynamic effect through sympathomimetic drive in hypotensive patients (32). However, multiple studies have shown that a subset of patients develop hypotension in temporal association with ketamine administration (33–36). There is some evidence that ketamine may cause myocardial depression, although the mechanism was not entirely elucidated (36,37).

The literature comparing etomidate with ketamine as induction for RSI has reported mixed results with regard to hemodynamic effects. There have been several observational analyses comparing etomidate and ketamine in various settings and results have been varied (6,35,38–47). There are limited randomized studies that compare ketamine and etomidate for emergency tracheal intubation, however, one large randomized trial suggested no difference in mortality outcome at 28 days (44,48–52). Other trials in settings outside of the ED have not found a significant difference in hemodynamic effect or maximum Sequential Organ Failure Assessment (SOFA) score in the first 3 days (48,50).

The aim of this study is to compare the effects of a single dose of ketamine vs. etomidate during RSI of critically ill patients in the ED on the maximum SOFA score, as well as incidence of hypotension.

MATERIALS AND METHODS

Trial Design and Setting

This single-center, parallel-group, randomized trial compared ketamine with etomidate for RSI in critically ill adults in the ED and was conducted from September 2013 through November 2015 in the ED of an urban, academic level I trauma center with more than 100,000 annual ED visits. All endotracheal intubations are performed by either emergency medicine residents (usually postgraduate year 3 or higher) or attending emergency physicians. All residents receive extensive training in endotracheal intubation, including didactics, hands-on sessions with all direct and video laryngoscopes, simulation sessions, and intubation of patients during rotations in community EDs earlier in training. Patients undergoing emergency endotracheal intubation are generally not able to provide informed consent. This trial, therefore, was conducted using Exception from Informed Consent (Food and Drug Administration [FDA] regulation 21 CFR 50.24) (53). Before the trial was initiated, we elicited feedback from potential participants and disclosed the study to the local community. First, we surveyed 252 ED patients or their family members. Second, we met with three local community groups and provided details on the trial and allowed for a prolonged period of asking and answering questions. Feedback was uniformly supportive of conducting the trial. We also publicly disclosed the details of the trial and offered opt-out bracelets to anyone who wished not to participate in the trial. The local Institutional Review Board approved the Exception from Informed Consent community consultation and public disclosure plan. After reviewing the results of these, they approved the study for enrollment. Before enrollment began, this trial was registered at ClinicalTrials.gov (NCT01823328). Enrollment began in September 2013 and the trial concluded in November 2015.

Patient Selection

ED patients 18 years and older undergoing RSI (defined as near-simultaneous administration of a sedative and neuromuscular blocking agent [NMBA]) were eligible. Exclusion criteria included patients with a condition in which an increase in heart rate or blood pressure would be hazardous, as judged by the treating physician (eg, aneurysmal subarachnoid hemorrhage or hypertensive emergency); patients known or suspected to have increased intracranial pressure; patients with a known contraindication or allergy to ketamine or etomidate; patients wearing a bracelet with the words “KvE declined”; patients who were prisoners or under arrest; and female patients of childbearing age, defined as 18–50 years old, and who did not have a documented negative pregnancy test during that ED encounter.

Before a protocol change during the trial, the first 103 patients enrolled using identical inclusion criteria but different exclusion criteria. The original exclusion criteria included patients with a known contraindication or allergy to ketamine or etomidate; patients wearing a bracelet with the words “KvE declined” (available to community members as part of the Exception from Informed Consent process); and patients who were prisoners or under arrest. The FDA mandated the additional exclusion criteria to exclude patients with a condition in which an increase in heart rate or blood pressure would be hazardous, patients known or suspected to have increased intracranial pressure, and female patients aged between 18 and 50 years unless a negative pregnancy test was documented. The exclusion criteria were added even though there are scant data showing that ketamine is contraindicated in the setting of elevated blood pressure, in head injury, and in women of childbearing age (54–56).

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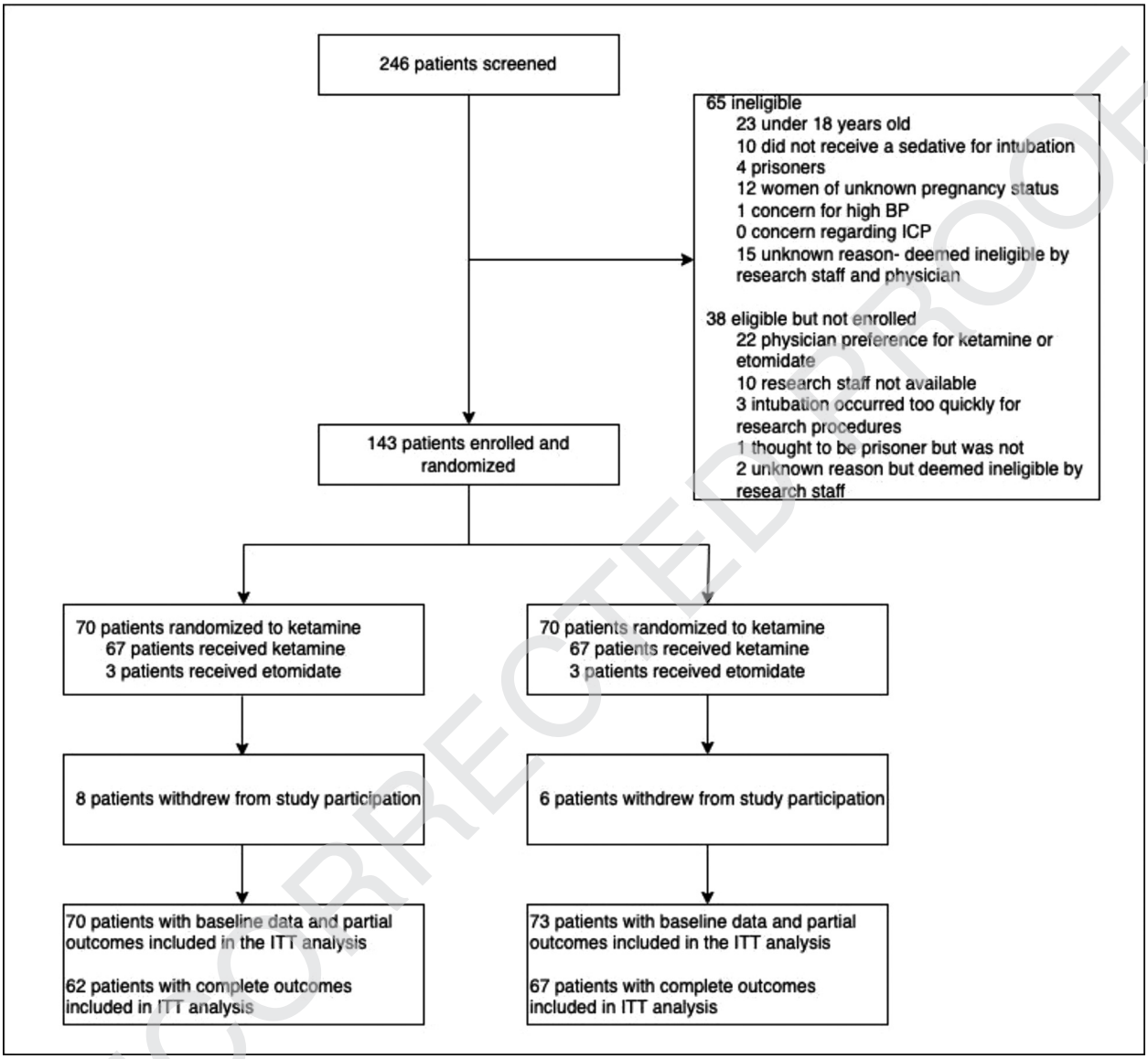

Figure 1. Flow chart of study participants. BP = blood pressure; ICP = intracranial pressure; ITT = intention to treat.

Randomization and Trial Procedures

Eligible patients were randomly assigned in a 1:1 ratio to receive ketamine (2 mg/kg) or etomidate (0.3 mg/kg) as the sedative, along with a physician-selected NMBA. If the patient weight was unknown at the time of intubation, an estimated weight was used. Randomization was performed before the start of the trial with the use of a computer-generated assignment sequence in permuted blocks of random sizes of 2, 4, 6, 8, and 10. Intervention assignments were placed inside a folded sheet of paper in sequentially numbered, opaque envelopes. A research associate opened the next envelope to determine intervention allocation after patient enrollment. Although the ED team was aware of the sedative received, the intensive care unit (ICU) team was blinded to treatment assignment. The exact medication received was not documented in the medication administration record; rather, a blinded study-specific order was placed and the drug administration information remained in research records only.

The remainder of the intubation procedure, including patient positioning, preoxygenation strategy, choice of neuromuscular blocking agent, choice of intubation devices, and post-intubation sedation, was at the discretion of the emergency physician. Subsequent ICU care was also left to the discretion of the treating team.

Measurements

Trained research staff prospectively collected process and outcome data from patient randomization until 1 min after the end of the first intubation attempt, including vital

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Table 1. Characteristics of the Patients at Baseline.

Characteristic	Ketamine (n = 70)	Etomidate (n = 73)
Age, y, median (IQR)	50 (32–65)	49 (31–58)
Male sex, n (%)	42 (60)	49 (67)
Weight, kg, median (IQR)	84 (75–100)	80 (70–96)
Race, n (%)		
White, non-Hispanic	43 (61)	39 (53)
Black, non-Hispanic	19 (27)	22 (30)
American Indian	7 (10)	3 (4)
Hispanic	1 (1)	4 (6)
Other/unknown	0	5 (7)
Medical comorbidities, n (%)		
Hypertension	20 (29)	24 (33)
Regular alcohol use	16 (23)	12 (16)
Smoking	13 (19)	13 (18)
Chronic renal failure	9 (13)	6 (8)
Chronic obstructive pulmonary disease	6 (9)	8 (11)
Stroke history	7 (10)	5 (7)
Heart failure	7 (10)	1 (1)
Coronary artery disease	6 (9)	2 (3)
Cancer	1 (1)	0
Human immunodeficiency virus infection	1 (1)	0
Primary indication for intubation, n (%)		
Medical	36 (51)	40 (55)
Overdose	14 (20)	14 (19)
Shock, septic	5 (7)	6 (8)
Seizure	4 (6)	3 (4)
Chronic obstructive pulmonary disease	3 (4)	3 (4)
Pneumonia	2 (3)	3 (4)
Other, medical	8 (11)	11 (15)
Trauma	17 (24)	12 (16)
Head injury	7 (10)	6 (8)
Other, trauma	10 (14)	6 (8)
Other	10 (14)	17 (23)
Unknown	7 (10)	4 (5)
Reason for emergency intubation, n (%)		
Airway protection	47 (67)	37 (51)
Respiratory failure	12 (17)	20 (27)
Anticipated clinical deterioration	5 (7)	10 (14)
Hypoxia	5 (7)	5 (7)
Cardiac arrest	1 (1)	1 (1)
Sedatives administered before arrival to the ED, n (%)		
Etomidate	0	0
Ketamine	1 (1)	7 (10)
One or more difficult airway characteristics, n (%)*	45 (64)	33 (45)
Sepsis criteria met,† n (%)	10 (14)	19 (26)

(*continued on next page*)

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Table 1. (*continued*)

Septic shock criteria met,‡ n (%)	6 (9)	10 (14)
Vital signs before intubation		
Temperature, °C, median (IQR)	36.6 (35.8–37.2)	36.3 (35.3–37.0)
Heart rate, beats/min, median (IQR)	98 (84–115)	105.5 (84–119)
Oxygen saturation, %, median (IQR)	98 (95–100)	98 (94–100)
Oxygen saturation < 90%, n (%)	5 (7)	6 (8)
SBP, mm Hg, median (IQR)	139 (128–161)	140 (119–167)
SBP < 90 mm Hg, n (%)	1 (1)	4 (5)
Glasgow Coma Scale score, median (IQR)	7 (6–12)	8 (6–11)

IQR = interquartile range; SBP = systolic blood pressure.
* Difficult airway characteristics included blood or vomit in airway, short neck, cervical immobilization, small mandible, obesity, airway edema or obstruction, facial trauma, and large tongue.
† Sepsis criteria as defined by two or more systemic inflammatory response syndrome criteria and antibiotics administered.
‡ Septic shock as defined by sepsis and systolic blood pressure < 90 mm Hg after 1 L of intravenous fluids.

signs at baseline and during intubation, and whether the attempt was successful. The starting and lowest oxygen saturation, blood pressure, and heart rate were collected, as were the highest blood pressure and heart rate until 1 min after the procedure.

After intubation, research staff recorded vital signs every 2 min until the patient left the ED or 1 h had passed, whichever came sooner. They also documented medications given for post-intubation sedation. After the procedure, the intubating physician recorded additional data on a standardized collection form, including indication for intubation, presence of difficult airway characteristics, details on the process of intubation, whether the patient had suspected sepsis or septic shock, and whether specific complications occurred, including hypersalivation, laryngospasm, witnessed aspiration during intubation, esophageal intubation, or other events the treating physician deemed to be a complication. Sepsis was defined as meeting at least two systemic inflammatory response syndrome criteria and receipt of intravenous antibiotics (57). Septic shock was defined as sepsis plus a systolic blood pressure of ≤ 90 mm Hg after 1 L of isotonic crystalloid fluid (58).

After the patient was discharged from the hospital, a trained research staff member, blinded to group assignment, reviewed the medical record to record the following data points: patient demographic characteristics, medical history, hypoxia during the first 2 h in the ICU; lowest blood pressure during the first 6 h in the ICU; all administrations of sedative medication in the first 6 h after intubation; the Sequential Organ Failure Assessment (SOFA) score at ED admission; the maximum SOFA score on hospital days 1, 2, and 3; corticosteroid administration in the first 96 h of hospitalization; vasopressor-free days, ventilator-free days, and ICU-free days up to day 28; number of days receiving antibiotic therapy; whether the patient was diagnosed with any infection; whether the patient received a blood transfusion; final diagnosis; and mortality at hospital discharge or 30 days, whichever occurred first (59). A second reviewer abstracted SOFA scores for 10% of enrolled patients to calculate interobserver agreement. The agreement for maximum SOFA score was 87%, with a κ value of 0.85, indicating almost perfect agreement (60).

Trial Outcomes

The primary outcome was the maximum SOFA score during the first 3 days of hospitalization, not including the SOFA score on arrival. This outcome has been used in prior trials comparing ketamine with etomidate (48). Serial measurement of the SOFA score has been found to correlate well with mortality (61).

Key exploratory outcomes included in-hospital 30-day mortality; successful intubation on the first attempt; hypoxemia (oxygen saturation < 90%) within 5 min of intubation or, separately, within the first 2 h of mechanical ventilation; and post-intubation hypotension (systolic blood pressure < 90 mm Hg) at any time after intubation while still in the ED, or, separately, within 6 h of intubation. We also defined several exploratory outcomes, including severe hypoxemia and number of sedative agent administrations (full details available in the Appendix). Q5

For the first portion of the trial, during enrollment of the first 103 patients, the primary outcome was mortality at hospital discharge or at 30 days. During the process of

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submitting the Investigational New Drug application for this study, as required by the FDA at the time for studies using Exception from Informed Consent (FDA 21 CFR 50.24), the outcome was changed to maximum SOFA score, selected as an outcome that correlated well with mortality (62).

Statistical Analysis

This study was powered to detect a 2-point between-group difference in maximum SOFA score, which has been deemed to be a clinically relevant difference between two treatment groups and has been used in prior trials (48,62). Therefore, to detect this difference with 80% power with a significance level of 0.05, enrollment of 126 patients with complete outcomes was required. We continued the trial until 126 patients had complete outcomes, excluding those who asked that trial procedures not continue after enrollment. For studies operating under FDA 21 CFR 50.24, data collected before patient withdrawal can be used, and the outcome of mortality can be collected after withdrawal through public records (63).

The principal trial analyses were performed in the intention-to-treat population that included all patients in the group they were assigned to, regardless of medication received. The primary outcome and exploratory outcomes were compared between groups by calculating the difference in the proportions or median difference, as appropriate, between groups, and the associated 95% CI. Hodges-Lehmann median between-group differences and the associated 95% CIs were calculated for continuous variables. The Wilcoxon rank sum test was used to calculate a single p value for the primary outcome. Between-group differences in exploratory outcomes are reported with the use of point estimates and 95% CIs. The widths of the CIs have not been adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between groups. No corrections were made for multiple comparisons. Stata, version 15.1 (StataCorp) was used for data analysis.

RESULTS

Trial Patients and Interventions

A total of 143 patients were enrolled, 70 randomized to ketamine and 73 randomized to etomidate. Figure 1 shows the flow of patients into the trial. Fourteen patients withdrew from the trial, so complete data are available for 129 patients, and partial data, including mortality, is available for 143 patients. The median age was 50 years and 36% were women. The two most common indications for intubation were trauma and overdose. Of the cohort, 20% of the patients had a suspicion of sepsis at the time of intubation. The remaining baseline characteristics and a full list of indications for intubation are shown in Table 1 and Supplementary Table 1.

A total of 67 patients (96%) in the ketamine group received ketamine for RSI; 71 patients (97%) in the etomidate group received etomidate for RSI. The remaining received the opposite medication based on clinical judgment of the treating physician. The median dose of ketamine was 2 mg/kg (IQR 2.0–2.1 mg/kg); the median dose of etomidate was 0.27 mg/kg (IQR 0.23–0.30 mg/kg) (Table 2).

More than 99% of patients received preoxygenation before intubation, and the median oxygen saturation before intubation was 100% (IQR 97–100%). A Macintosh video laryngoscope was used for 66 patients (94%) in the ketamine group and for 64 patients (88%) in the etomidate group. Further detail on the intubation procedure is shown in Table 2.

Main Results

There were a total of 62 patients (89%) in the ketamine group and 67 patients (92%) who did not withdraw and had the primary outcome of maximum SOFA score recorded. The median maximum SOFA score was 6.5 (IQR 5–9) in the ketamine group and 7 (IQR 5–9) in the etomidate group. There was no significant difference between the two groups, median difference of –0.2 (95% CI –1.4 to 1.1; $p = 0.79$).

Secondary Outcomes

First attempt success was 94% in the ketamine group and 89% in the etomidate group (difference 5%; 95% CI –4% to 13%). The incidence of hypotension in the ED was 28% in the ketamine group and 26% in the etomidate group (difference 2%; 95% CI –13% to 17%). There was no difference in corticosteroid administration in the first 96 h of hospitalization, with 15% in the ketamine group and 12% in the etomidate group receiving any corticosteroid (difference 3%; 95% CI –9% to 14%). There were no significant differences in ICU outcomes, including vasopressor-free days, ventilator-free days, and ICU free days. Thirty-day mortality for the ketamine group was 8 deaths (11%) and etomidate was 15 deaths (21%), which was not statistically different. Other study outcomes are shown in Table 3 and Supplementary Table 2.

DISCUSSION

In this single-center, partially blinded, randomized trial in the ED comparing ketamine with etomidate for RSI,

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Table 2. Characteristics of the Intubation Procedure.

Characteristic	Ketamine (n = 70)	Etomidate (n = 73)
Before induction		
Preoxygenation method, n (%)		
Nonrebreather	41 (60)	40 (55)
Bag valve mask ventilation	21 (31)	27 (37)
Noninvasive ventilation	3 (4)	6 (8)
Nasal cannula	2 (3)	0
None	1 (1)	0
Intubation position, ear to sternal notch or ramped, n (%)	54 (77)	54 (74)
Apneic oxygenation performed, n (%)	39 (56)	42 (58)
Induction		
Oxygen saturation at induction, %, median (IQR)	100 (98–100)	100 (96–100)
Sedative agent administered, n (%)		
Ketamine	67 (96)	2 (3)
Dose, mg/kg, median (IQR)	2.0 (2.0–2.1)	2.0 (1.0–3.0)
Etomidate	3 (4)	71 (97)
Dose, mg/kg, median (IQR)	0.27 (0.23–0.30)	0.27 (0.16–0.35)
Co-administration of neuromuscular blocking agent, n (%)	68 (97)	72 (99)
Succinylcholine	63 (90)	68 (93)
Rocuronium	5 (7)	4 (5)
After induction		
Device used on first attempt, n (%)		
Macintosh video laryngoscope	66 (94)	64 (88)
Direct laryngoscope	3 (4)	2 (4)
AirTraq	1 (1)	1 (1)
Intubating laryngeal mask airway	1 (1)	3 (4)
Glidescope video laryngoscope	1 (1)	1 (1)
Blind nasotracheal intubation	0	1 (1)
Bougie used during the successful attempt, n (%)	60 (86)	54 (74)
Cormack-Lehane grade, n (%)		
1 (complete view)	39 (56)	43 (59)
2	19 (27)	24 (33)
3	10 (14)	6 (8)
4 (most obstructed view)	2 (3)	0

IQR = interquartile range.

we did not observe a difference between the two medications for the primary outcome of maximum SOFA score during the first 3 days of hospitalization. Rates of secondary outcomes, including post-intubation hypotension, first-attempt intubation success, and mortality did not differ between groups. Although this trial was relatively small and underpowered to detect small differences between groups in these exploratory outcomes, these data argue against the presence of a large difference in patient-centered outcomes between the two medications.

Prior research comparing ketamine and etomidate is mixed, although prior randomized trials comparing ketamine or a ketamine/propofol mixture with etomidate have shown no important differences between groups for endotracheal intubation (47,48,50–52). The largest and most recent trial randomized 801 patients to receive ketamine or etomidate for RSI in the ICU, primarily by an anesthesia-based airway team. Seven-day survival was higher for the ketamine group, however, this difference was not observed at day 28 and no significant differences

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Table 3. Outcomes.

Outcome	Ketamine (n = 70)	Etomidate (n = 73)	Absolute Risk Difference or Difference in Medians (95% CI)
Primary outcome			
Maximum SOFA score during first 3 d of hospitalization, median (IQR)*	6.5 (5–9) [n = 62]	7 (5–9) [n = 67]	0 (–1 to 1)
Prespecified exploratory outcomes			
First attempt success, proportion, n (%)	66 (94)	65 (89)	5 (–4 to 13)
Hypoxemia, oxygen saturation < 90% during or within 5 min of intubation, %, n/N with available data (%)	8/67 (12)	14/72 (19)	–8 (–19 to 4)
Hypotension in the ED after intubation, proportion, n/N with available data (%)†	19/67 (28)	19/72 (26)	2 (–13 to 17)
Hypotension† in the first 6 h after intubation, (%)	28 (42)	34 (47)	–7 (–23 to 10)
Death before 30 d or hospital discharge, n (%)	8 (11)	15 (21)	–9 (–21 to 3)
Death in patients with sepsis patients, n (%)	1/10 (10)	4/19 (21)	–11 (–37 to 15)
Post-hoc exploratory outcomes			
Vasopressor-free days, median (IQR)	28 (28–28)	28 (28–28)	0
Ventilator-free days, median (IQR)	27 (24–47)	27 (25–27)	0
ICU-free days, median (IQR)	26 (23–27)	26 (25–27)	0 (–1 to 0)

ED = emergency department; ICU = intensive care unit; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.

* 14 patients elected to withdraw from chart review so the primary outcome excluded these patients. The emergency department data collected prior to withdrawal are included for those variables.

† Hypotension as defined by systolic blood pressure < 90 mm Hg.

were found in secondary outcomes, including ICU length of stay, duration of mechanical ventilation, SOFA scores, or vasopressor requirements (51). Jabre et al. conducted a 655-patient, randomized trial that enrolled critically ill adult patients to receive ketamine or etomidate for RSI, and demonstrated no difference in maximum SOFA score or other secondary outcomes, including mortality, however, the cohort had higher SOFA scores than in this RCT (10.3 vs. 9.6) (48). Smischney et al. analyzed 152 adult ICU patients who received either a combination of reduced-dose ketamine and propofol or etomidate, and observed no difference in post-intubation blood pressure or rate of vasopressor administration (50). All prior randomized studies have been in ICU settings vs. this study in the ED. No significant differences were found in either.

In general, observational studies comparing etomidate and ketamine have had mixed results. A recent analysis of 6806 patients in the National Emergency Airway Registry found slight increase in hypotension with use of ketamine (adjusted odds ratio 1.4; 95% CI 1.2–1.7). There was no difference is peri-intubation mortality or first-pass success (6). A large retrospective study of 7466 patients in an air medical airway system found ketamine use was associated with increased hypotension with no difference in first-pass success (38). However, smaller retrospective studies offer conflicting results, with one finding no difference in hemodynamics between ketamine and etomidate, and one finding ketamine was associated with a decreased risk of hypotension compared with etomidate (39,43). Thus, although some observational studies suggest ketamine may have a higher incidence of post-intubation hypotension, this has not been borne out in randomized trials, including our own. In general, prior studies also showed no significant difference in mortality outcomes between etomidate and ketamine when used for emergency intubations (16,35,41).

This study, combined with our interpretation of the previous literature we identified, found that there is not clear evidence that either etomidate or ketamine is superior to the other for use in emergency tracheal intubation. There was no difference with regard to maximum SOFA score, first-pass success, or mortality. Both medications appear to have adequate efficacy for use in RSI in the ED and clinicians can safely choose either agent. It should be noted

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that etomidate has a shorter duration of action than ketamine, which necessitates more rapid administration of post-intubation sedation. Further randomized trials with greater numbers of participants will be essential to elucidate any differences in outcomes that could potentially exist between ketamine and etomidate for use in emergency tracheal intubation.

Limitations

There are several limitations to this randomized controlled trial. First, all patients requiring intubation were enrolled in the trial rather than only enrolling patients at higher risk for harm from cardiovascular collapse. Therefore, these results may not generalize to centers that care for patients with a higher likelihood of shock, sepsis, or hypotension. Second, we excluded women of childbearing age in the latter one-half of the trial (FDA stipulation). This may limit generalizability, although this limitation only applies to the last 40 patients enrolled. Third, the primary outcome for this trial was maximum SOFA score, which itself is not a patient-centered outcome, but has been shown to correlate with patient-centered outcomes, such as mortality (61). Fourth, emergency physicians were unblinded, which may alter post-intubation care in the ED, however, this is mitigated by the blinding of ICU physicians. Fifth, 7 years have elapsed since the trial concluded. However, sedation practices for RSI have not changed substantially and ketamine and etomidate remain the two most commonly used drugs (6). The clinical question remains pertinent, with at least one ongoing randomized trial studying this exact question (ClinicalTrials.gov number NCT05277896) (64).

CONCLUSIONS

Among critically ill adults undergoing tracheal intubation in the ED, there was no difference in maximum SOFA scores between the use of ketamine vs. etomidate. Based on current evidence, either agent is appropriate for use in RSI in critically ill ED patients.

Declaration of Competing Interest

Q6 None.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jemermed.2023.06.009.

REFERENCES

1. Brown 3rd CA, Bair AE, Pallin DJ, et al. Techniques, success, and adverse events of emergency department adult intubations. Ann Emerg Med 2015;65:363–70 .e1.
2. Okubo M, Gibo K, Hagiwara Y, et al. The effectiveness of rapid sequence intubation (RSI) versus non-RSI in emergency department: an analysis of multicenter prospective observational study. Int J Emerg Med 2017;10:1.
3. Mort TC. Complications of emergency tracheal intubation: hemodynamic alterations—part I. J Intensive Care Med 2007;22:157–65.
4. Sagarin MJ, Barton ED, Chng Y-M, et al. Airway management by US and Canadian emergency medicine residents: a multicenter analysis of more than 6,000 endotracheal intubation attempts. Ann Emerg Med 2005;46:328–36.
5. Yeung JK, Zed PJ. A review of etomidate for rapid sequence intubation in the emergency department. CJEM 2002;4:194–8.
6. April MD, Arana A, Schauer SG, et al. Ketamine versus etomidate and peri-intubation hypotension: a National Emergency Airway Registry Study. Acad Emerg Med 2020;27:1106–15.
7. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. Anaesthesia 1984;39:973–81.
8. Cherfan AJ, Tamim HM, AlJumah A, et al. Etomidate and mortality in cirrhotic patients with septic shock. BMC Clin Pharmacol 2011;11:22.
9. Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis*. Crit Care Med 2012;40:2945–53.
10. Cuthbertson BH, Sprung CL, Annane D, et al. The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. Intensive Care Med 2009;35:1868–76.
11. Lipiner-Friedman D, Sprung CL, Laterre PF, et al. Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med 2007;35:1012–18.
12. Sunshine JE, Deem S, Weiss NS, et al. Etomidate, adrenal function, and mortality in critically ill patients. Respir Care 2013;58:639–46.
13. Tekwani KL, Watts HF, Chan CW, et al. The effect of single-bolus etomidate on septic patient mortality: a retrospective review. West J Emerg Med 2008;9:195–200.
14. Wagner RL, White PF, Kan PB, et al. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1984;310:1415–21.
15. Albert SG, Ariyan S, Rather A. The effect of etomidate on adrenal function in critical illness: a systematic review. Intensive Care Med 2011;37:901–10.
16. Bruder EA, Ball IM, Ridi S, et al. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database Syst Rev 2015;1.
17. Gu W-J, Wang F, Tang L, et al. Single-dose etomidate does not increase mortality in patients with sepsis: a systematic review and meta-analysis of randomized controlled trials and observational studies. Chest 2015;147:335–46.
18. Ray DC, McKeown DW. Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. Crit Care 2007;11:R56.
19. Tekwani KL, Watts HF, Rzechula KH, et al. A prospective observational study of the effect of etomidate on septic patient mortality and length of stay. Acad Emerg Med 2009;16:11–14.
20. Ehrman R, Wira C, Lomax A, et al. Etomidate use in severe sepsis and septic shock patients does not contribute to mortality. Intern Emerg Med 2011;6:253–7.
21. Alday NJ, Jones GM, Kimmons LA, et al. Effects of etomidate on vasopressor use in patients with sepsis or severe sepsis: a propensity-matched analysis. J Crit Care 2014;29:517–22.

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22. McPhee LC, Badawi O, Fraser GL, et al. Single-dose etomidate is not associated with increased mortality in ICU patients with sepsis: analysis of a large electronic ICU database. Crit Care Med 2013;41:774–83.
23. Hohl CM, Kelly-Smith CH, Yeung TC, et al. The effect of a bolus dose of etomidate on cortisol levels, mortality, and health services utilization: a systematic review. Ann Emerg Med 2010;56:105–13 .e5.
24. Dmello D, Taylor S, O'Brien J, et al. Outcomes of etomidate in severe sepsis and septic shock. Chest 2010;138:1327–32.
25. Tekwani KL, Watts HF, Sweis RT, et al. A comparison of the effects of etomidate and midazolam on hospital length of stay in patients with suspected sepsis: a prospective, randomized study. Ann Emerg Med 2010;56:481–9.
26. Payen J-F. Etomidate for critically ill patients: let us clarify the debate. Eur J Anaesthesiol 2012;29:504–5.
27. April MD, Arana A, Pallin DJ, et al. Emergency department intubation success with succinylcholine versus rocuronium: a National Emergency Airway Registry study. Ann Emerg Med 2018;72:645–53.
28. April MD, Schauer SG, Brown Rd CA, et al. A 12-month descriptive analysis of emergency intubations at Brooke Army Medical Center: a National Emergency Airway Registry study. US Army Med Dep J 2017(3–17):98–104.
29. Bokoch MP, Eilers H. Intravenous anesthetics. In: Pardo MC, Miller RD, editors. Basics of Anesthesia. Elsevier; 2018. p. 104–12.
30. Kim JM, Shin TG, Hwang SY, et al. Sedative dose and patient variable impacts on postintubation hypotension in emergency airway management. Am J Emerg Med 2019;37:1248–53.
31. Smischney NJ, Seisa MO, Heise KJ, et al. Practice of intubation of the critically ill at Mayo Clinic. J Intensive Care Med 2019;34:204–11.
32. Merelman AH, Perlmutter MC, Strayer RJ. Alternatives to rapid sequence intubation: contemporary airway management with ketamine. West J Emerg Med 2019;20:466–71.
33. Groth CM, Acquisto NM, Khadem T. Current practices and safety of medication use during rapid sequence intubation. J Crit Care 2018;45:65–70.
34. Tarquinio KM, Howell JD, Montgomery V, et al. Current medication practice and tracheal intubation safety outcomes from a prospective multicenter observational cohort study. Pediatr Crit Care Med 2015;16:210–18.
35. Upchurch CP, Grijalva CG, Russ S, et al. Comparison of etomidate and ketamine for induction during rapid sequence intubation of adult trauma patients. Ann Emerg Med 2017;69:24–33 .e2.
36. Miller M, Kruit N, Heldreich C, et al. hemodynamic response after rapid sequence induction with ketamine in out-of-hospital patients at risk of shock as defined by the shock index. Ann Emerg Med 2016;68:181–8 .e2.
37. Pagel PS, Kampine JP, Schmeling WT, et al. Ketamine depresses myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs with autonomic nervous system blockade. Anesthesiology 1992;76:564–72.
38. Pollack MA, Fenati GM, Pennington TW, et al. The use of ketamine for air medical rapid sequence intubation was not associated with a decrease in hypotension or cardiopulmonary arrest. Air Med J 2020;39:111–15.
39. Price B, Arthur AO, Brunko M, et al. Hemodynamic consequences of ketamine vs etomidate for endotracheal intubation in the air medical setting. Am J Emerg Med 2013;31:1124–32.
40. Patanwala AE, McKinney CB, Erstad BL, et al. Retrospective analysis of etomidate versus ketamine for first-pass intubation success in an academic emergency department. Acad Emerg Med 2014;21:87–91.
41. Baekgaard JS, Eskesen TG, Moo Lee J, et al. Ketamine for rapid sequence intubation in adult trauma patients: a retrospective observational study. Acta Anaesthesiol Scand 2020;64:1234–42.
42. Mohr NM, Pape SG, Runde D, et al. Etomidate use is associated with less hypotension than ketamine for emergency department sepsis intubations: a NEAR Cohort Study. Acad Emerg Med 2020;27:1140–9.
43. Van Berkel MA, Exline MC, Cape KM, et al. Increased incidence of clinical hypotension with etomidate compared to ketamine for intubation in septic patients: a propensity matched analysis. J Crit Care 2017;38:209–14.
44. Farrell NM, Killius K, Kue R, et al. A comparison of etomidate, ketamine, and methohexital in emergency department rapid sequence intubation. J Emerg Med 2020;59:508–14.
45. Sivilotti MLA, Filbin MR, Murray HE, et al. Does the sedative agent facilitate emergency rapid sequence intubation? Acad Emerg Med 2003;10:612–20.
46. Stanke L, Nakajima S, Zimmerman LH, et al. Hemodynamic effects of ketamine versus etomidate for prehospital rapid sequence intubation. Air Med J 2021;40:312–16.
47. Foster M, Self M, Gelber A, et al. Ketamine is not associated with more post-intubation hypotension than etomidate in patients undergoing endotracheal intubation. Am J Emerg Med 2022;61:131–6.
48. Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet 2009;374:293–300.
49. Disel NR, Yilmaz HL, Sertdemir Y, et al. Etomidate versus ketamine: effective use in emergency procedural sedation for pediatric orthopedic injuries. Pediatr Emerg Care 2016;32:830.
50. Smischney NJ, Nicholson WT, Brown DR, et al. Ketamine/propofol admixture vs etomidate for intubation in the critically ill: KEEP PACE Randomized clinical trial. J Trauma Acute Care Surg 2019;87:883–91.
51. Matchett G, Gasanova I, Riccio CA, et al. Etomidate versus ketamine for emergency endotracheal intubation: a randomized clinical trial. Intensive Care Med 2022;48:78–91.
52. Baradari AG, Firouzian A, Kiasari AZ. Effect of etomidate versus combination of propofol-ketamine and thiopental-ketamine on hemodynamic response to laryngoscopy and intubation: a randomized double blind clinical trial. Anesth Pain Med 2016;6(1):e30071.
53. CFR – Code of Federal Regulations Title 21. US Food and Drug Administration; 2023 Accessed July 11 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=50.24 .
54. Rosenbaum SB, Gupta V, Patel P, et al. Ketamine. StatPearls Publishing; 2022.
55. Zeiler FA, Teitelbaum J, West M, et al. The ketamine effect on ICP in traumatic brain injury. Neurocrit Care 2014;21:163–73.
56. Chomchai S, Phuditshinnapatra J, Mekavuthikul P, et al. Effects of unconventional recreational drug use in pregnancy. Semin Fetal Neonatal Med 2019;24:142–8.
57. Kaukonen K-M, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015;372:1629–38.
58. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327.
59. Thompson Bastin ML, Baker SN, Weant KA. Effects of etomidate on adrenal suppression: a review of intubated septic patients. Hosp Pharm 2014;49:177–83.
60. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

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61. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754–8.
62. Moreno R, Vincent J-L, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Intensive Care Med 1999;25:686–96.
63. . Exception from Informed Consent Requirements for Emergency Research, Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors. US Food and Drug Administration; April 19, 2021 Accessed https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research .
64. Randomized Trial of Sedative Choice for Intubation. ClinicalTrials.gov. Accessed February 22, 2023. https://clinicaltrials.gov/ct2/show/NCT05277896?term=ketamine+etomidate+vanderbilt&draw=2&rank=1.

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ARTICLE SUMMARY

1. Why is this topic important?

Rapid sequence intubation (RSI) is a widely used technique in emergency airway management. Induction agents may have differential effects in critical illness and the most used agents are ketamine and etomidate.

2. What does this study attempt to show?

This study aims to investigate whether the use of ketamine vs. etomidate for RSI induction in critically ill patients results in different maximal Sequential Organ Failure Assessment (SOFA) scores.

3. What are the key findings?

There was no significant difference in maximal SOFA score or the secondary outcomes of post-intubation hypotension or mortality between ketamine and etomidate for RSI induction.

4. How is patient care impacted?

Based on current evidence, either ketamine or etomidate can be used as the induction agent for rapid sequence intubation in the emergency department.

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