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A retrospective data analysis on the induction medications used in trauma rapid sequence intubations and their effects on outcomes

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Abstract

Purpose Rapid sequence intubation (RSI) in trauma patients is common; however, the induction agents used have been debated. We determined which induction medications were used most frequently for adult trauma RSIs and their associations with hemodynamics and outcomes. We hypothesized that etomidate is the most commonly used induction agent and has similar outcomes to other induction agents.

Methods This retrospective review at two U.S. level I trauma centers evaluated adult trauma patients undergoing RSI within 24 h of admission, between 01/01/2016 and 12/31/2017. We compared patient characteristics and outcomes by induction agent. Comparisons on the primary outcome of in-hospital mortality and secondary outcomes of peri-intubation hypotension, hospital and ICU length of stay (LOS), ventilator days, and complications used logistic regression or negative binomial regression. Regression models adjusted for hospital site, age, patient severity measures, and intubation location.

Results Among 1303 trauma patients undergoing RSI within 24 h of admission, 948 (73%) were intubated in the emergency department (ED) and 325 (25%) in the operating room (OR). The most common induction agents were etomidate (68%), propofol (17%), and ketamine (11%). In-hospital mortality was highest in the etomidate group (25.5%), followed by ketamine (17%), and propofol (1.8%).

Conclusion Etomidate was most commonly used in ED intubations; propofol was most used in the OR. Compared to propofol, patients induced with etomidate had higher mortality and complication rates. Findings should be interpreted with caution given limited generalizability and residual confounding by indication.

Keywords Trauma · Rapid sequence intubation · Induction agents

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Background

Although performing rapid sequence intubations (RSI) in the emergency department (ED) and operating room (OR) is a common occurrence in trauma patients, there are few guidelines that recommend a specific induction agent of choice [1–3]. Trauma patients are prone to hypotension, aspiration, hypoxemia, and traumatic brain and cervical injuries, making airway management challenging. Induction agents should create optimal conditions in a short amount of time and avoid secondary insult to injuries while maintaining hemodynamic stability [1]. Prompt establishment of a definitive airway while maintaining sufficient oxygenation is associated with favorable outcomes [2]. The following induction agents may be used for RSI: propofol, ketamine,

methohexital, midazolam, and etomidate. However, each of these agents is associated with its own side effects [3].

In many centers, etomidate is the drug of choice for RSI due to its quick onset and hemodynamic stability [2]. However, its use in trauma patients has been questioned due to its association with adverse effects such as adrenal insufficiency, acute respiratory distress syndrome, and multiple-organ dysfunction syndrome [4, 5]. Ketamine has been gaining popularity for use in unstable trauma patients, despite the risk of hypotension when it is used in a catecholamine-depleted state [6, 7]. The concern for ketamine use is its potential to increase intracranial pressure in the setting of traumatic brain injury (TBI). However, several studies have not reported significant effects on intracranial pressure [8, 9]. Propofol may be considered in normotensive patients, but it may cause profound hypotension [10, 11].

There currently exists insufficient evidence for trauma guidelines to recommend a specific first-line induction agent for trauma RSIs. In fact, the Eastern Association for the Surgery of Trauma (EAST) guidelines state: “There are no recommendations regarding the use of specific induction agents used for RSI in trauma [2].” Furthermore, the available literature on induction drugs used in trauma RSIs, or comparing outcomes between various agents, is scarce and based on low-powered studies. The purposes of this study were the following: (1) determine the most commonly used induction agent; (2) compare differences between ED and OR practices; and (3) compare outcomes such as mortality among the agents used in trauma RSIs at two level I trauma centers in California. Our hypothesis is that etomidate is the most commonly used induction agent and will have similar outcomes compared to other induction agents.

Methods

Institutional Review Board (IRB) approval was obtained prior to performing a multicenter, retrospective review of two level I trauma centers: The Los Angeles County + University of Southern California (USC) Medical Center and University of California, Irvine. Due to the retrospective nature and use of de-identified data, written informed consent was waived by the IRB. This manuscript followed the pertinent guidelines outlined in the statement of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Both centers’ trauma registries were queried, and trauma patients ≥ 18 years of age who underwent RSI within 24 h of admission, either in the ED or OR between January 01, 2016 to November 26, 2017, were included. RSI was confirmed by intubation procedure note documentation; if an RSI was not performed or the data was missing, the patient was excluded. Patients who were intubated in the field, at

an outside hospital prior to arriving to the study hospital, or were intubated at our hospitals without induction medications (i.e., patients in cardiac arrest), were excluded.

The primary outcome was in-hospital mortality. Secondary outcomes included the following: hospital length of stay (LOS), intensive care unit (ICU) LOS, mechanical ventilation (MV) days, peri-intubation hypotension (defined as a systolic blood pressure (SBP) < 90 mmHg), and vasopressor use during the 30-min post-intubation period and 24-h post intubation, complications (i.e., adrenal insufficiency, pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, etc., as documented in the chart by the International Classification of Diseases, Tenth Revision (ICD10) diagnosis codes), and discharge disposition.

Patient demographics (age, race, sex) and injury characteristics (mechanism of injury, revised trauma score (RTS), injury severity score (ISS), presence of TBI (defined by the ICD10 diagnosis codes) were also collected. Data on comorbid conditions, the induction and neuromuscular blocking agents used, the first ED vital signs (SBP, diastolic blood pressure (DBP), and heart rate (HR)), pre-intubation shock index (HR/SBP), location of intubation (ED, OR, ICU, other), specialty of provider intubating patient (ED, anesthesia, surgery), level of training of person performing intubation (attending, fellow, resident, student, etc.), and first pass success rate were also obtained. Peri-intubation hemodynamics (pre-intubation, and 5-, 15-, and 30-min post-intubation) were also documented. Intraoperative hemodynamic values were continuously measured and documented in the patient’s anesthetic electronic medical record. Of note, non-operative records did not always have values exactly at these times, so we used the values measured as close as possible to these times (i.e., if we were looking for the 15-min post-intubation values and there were only vitals recorded for 22 min, we used this as a surrogate for the 15-min value). The hemodynamic values were obtained from the vital signs transcribed in the patient’s electronic medical record. All of the data were recorded using a secure electronic database collection tool known as REDCap™ (version 10.8.4) [12].

Statistical analysis

Descriptive statistics were reported as median with interquartile range (IQR) or as frequencies and percentages for continuous variables and categorical variables, respectively. For the subset of patients induced with propofol, ketamine, or etomidate, differences in patient characteristics and outcomes by induction agent were tested by Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables. Post hoc multiple comparisons were performed for variables with significant global p -values using the Dwass–Steel–Critchlow–Fligner (DSCF) or Bonferroni correction methods for continuous and categorical variables,

respectively. Differences in the median change in HR, SBP, and DBP at 30 min post induction from pre-induction were also tested for each induction agent used by the Wilcoxon signed rank test.

To test for induction agent differences in the total number of intensive care unit (ICU) days, total hospital length of stay (LOS), days on MV, and complications, a negative binomial regression was conducted to account for the overdispersion of the data. An offset term of log (person-time) was fitted in the model for complication rate to allow for the varying person-time at risk for a complication event. Differences in the odds of in-hospital mortality, hypotension 24-h post-intubation, vasopressor requirement 24 h post-intubations, the presence of complications, and discharge disposition home were each tested by binary logistic regression. All models were adjusted for hospital site, age, injury severity score (ISS), revised trauma score (RTS), traumatic brain injury (TBI), and intubation location (ED vs. OR). In a sensitivity analysis, outcome comparisons were also conducted among a more homogenous subgroup of patients with ISS > 16.

For the subgroup of patients intubated in the OR or ED, differences in patient and provider characteristics by intubation location were tested by Wilcoxon rank sum test and χ^2 test, as appropriate. Differences in patient outcomes for in-hospital mortality, hypotension 24 h post-intubation, vasopressor requirement 24 h post-intubation, and the presence of complications by intubation location were tested by the Cochran–Mantel–Haenszel test, adjusting for hospital site.

All statistical analyses were performed using SAS 9.4 and Stata 15.

Results

Patient characteristics and demographics

We identified 1476 adult trauma patients undergoing RSI within 24 h of admission. Of these, 173 patients were excluded from analysis due to being field intubations, not meeting inclusion criteria, and/or were missing pertinent data. The median age was 41-years-old, there were 1051 (80.6%) patients who were male, and the most common ethnic/race group was Hispanic (603, 46.3%). There were more blunt injuries (1009, 77.5%), with the most common mechanism of injury being traffic-related (541, 41.5%). The median (IQR) RTS was 6.90 (5.97–7.84). Of the 1303 patients, 635 (49.8%) suffered from a TBI. The median (IQR) pre-intubation shock index was 0.72 (0.58–0.94; Table 1).

The patient characteristics varied when compared amongst the following three most commonly used induction medications: propofol, etomidate and ketamine. Patients receiving etomidate were the oldest, had a normal shock index, had the lowest median RTS, had severe trauma with

a median ISS of 17 (IQR 9–29), and had the highest percentage of patients with TBI (551, 63.5%). Patients receiving ketamine had a high shock index (median 0.81; IQR 0.65–1.05), the highest ISS (median 22, IQR 13–29), and had the second largest TBI population (37, 26.1%). The propofol group had the youngest patients, normal shock index, lowest number of TBI patients (25, 11.2%), and had the least severe ISS (median 10, IQR 8–17; Table 2).

Induction and neuromuscular blocking agents used

There were 948 (73%) and 325 (25%) patients intubated in the ED and in the OR, respectively. The most common induction agents used were etomidate (864, 67.8%), propofol (224, 17.2%), and ketamine (144, 11.1%) (Table 3). In the ED, the most common induction agent used was etomidate (849, 89.6%), ketamine (68, 7.2%), and propofol (5, 0.5%). In the OR, the most common agent used was propofol (219, 67.4%), followed by ketamine (76, 23.4%), and etomidate (15, 4.6%). There were 103 patients who were intubated with neuromuscular blocking agents only. The most commonly used neuromuscular blocking agent was succinylcholine (805, 61.8%), followed by rocuronium (427, 32.8%); both the ED and OR preferred succinylcholine as the first-line neuromuscular blocking agent, followed by rocuronium for RSIs (Table 3).

Primary outcome: in-hospital mortality

Of the entire study population, 275 (21.1%) had in-hospital mortality (Table 1). Etomidate was associated with the highest in-hospital mortality (226, 25.5%), followed by ketamine (25, 17%), and propofol (4, 1.8%) (Table 2). Compared to patients induced with propofol, the odds of in-hospital mortality were 4.7 (95% CI 1.2, 18.5) and 3.2 (95% CI 0.9, 11.9) times greater for patients induced with etomidate and ketamine, respectively, after adjusting for hospital site, age, ISS, RTS, TBI and intubation location (etomidate comparison Bonferroni-adjusted $p < 0.05$) (Table 4).

Secondary outcomes: hospital and ICU LOS, complications, MV days, peri-intubation hemodynamics, and discharge disposition home

Of the 1303 patients, 374 (30.3%) experienced hypotension and 266 (22.3%) required a vasopressor at 24-h post-intubation (Table 1). Etomidate was associated with an increase in SBP on first measurement after induction. Propofol was associated with the greatest decrease in 30-min post-induction SBP and DBP compared to ketamine and etomidate, but no clinically significant hypotension as all the SBP readings were > 90 mmHg (Table 2).

Table 1 Patient demographics and outcomes ($n = 1303$)

Patient demographics	Patients n (%)
Hospital site	
USC	912 (70%)
UCI	391 (30%)
Age ^a	41 (27–58)
Male	1050 (80.6%)
Race	
Caucasian	370 (28.4%)
Hispanic	603 (46.3%)
Asian	137 (10.5%)
African American	114 (8.8%)
Other	79 (6.1%)
Mechanism of injury	
Fall	322 (24.7%)
Traffic	541 (41.5%)
Stab	111 (8.5%)
Gunshot wound	162 (12.4%)
Assault with blunt object	76 (5.8%)
Other	91 (7.0%)
Type of injury	
Blunt	1009 (77.5%)
Penetrating	293 (22.5%)
Revised trauma score ^a	6.9 (5.97–7.84)
Injury severity score ^a	17 (9–26)
Traumatic brain injury	635 (49.8%)
Pre-intubation shock index ^a	0.72 (0.58–0.94)
Need for blood transfusion within 24 h	478 (37.6%)
Outcome	Patient n (%)
In-hospital mortality	275 (21.1%)
Total hospital LOS ^b	9 (0–286)
ICU LOS ^b	5 (0–183)
Mechanical ventilation days ^b	3 (0–130)
Hypotension 24 h post intubation	374 (30.3%)
Vasopressor requirement 24 h post intubation	266 (22.3%)
Experienced complication	832 (63.9%)
Number of complications ^b	1 (0–8)
Discharge dispositions	
Home with/without services	490 (37.6%)
Other healthcare facilities	449 (34.5%)
Mortality	282 (21.6%)
Unknown/other	42 (3.2%)

Demographics from 1303 trauma patients who underwent RSI within 24 h of admission

USC University of Southern California; UCI University of California, Irvine; LOS length of stay; ICU intensive care unit

^aMedian (25th, 75th percentile)

^bResults reported as median (range)

The median hospital and ICU LOS were 9 and 5 days, respectively. The median MV days was 3 days (Table 1). After adjusting for hospital site, age, ISS, RTS, TBI, and

intubation location, there were no statistically significant differences among induction agents on hospital and ICU LOS or mechanical ventilation days. Compared to induction with

Table 2 Patient characteristics by induction agent used (*n* = 1260)

Characteristic	Induction agent			<i>p</i> -value
	Propofol (<i>n</i> = 226)	Ketamine (<i>n</i> = 147)	Etomidate (<i>n</i> = 887)	
Age, years	34 (24–49) ^{a,b}	39 (27–53) ^a	44 (29–62)	< 0.001
Age, years				
18–35	123 (54.4%)	64 (43.5%)	330 (37.2%)	
35–65	85 (37.6%)	71 (48.3%)	373 (42.1%)	< 0.001
> 65	18 (8.0%)	12 (8.2%)	184 (20.7%)	
Pre-intubation shock index	0.73 (0.60–0.90) ^b	0.81 (0.65–1.05) ^a	0.72 (0.57–0.95)	0.01
Pre-intubation shock index				
0–0.5	25 (11.4%)	17 (12.4%)	136 (16.3%)	
0.5–1.0	163 (74.4%)	80 (58.4%)	524 (62.6%)	0.002
> 1.0	31 (14.2%)	40 (29.2%)	177 (21.2%)	
Revised trauma score	7.84 (7.84–7.84) ^{a,b}	7.70 (6.38–7.84) ^a	6.00 (5.00–7.84)	< 0.001
Revised trauma score				
0–6	7 (3.1%)	29 (21.0%)	444 (51.8%)	
6–7	13 (5.8%)	28 (20.3%)	171 (20.0%)	< 0.001
> 7	205 (91.1%)	81 (58.7%)	242 (28.2%)	
Traumatic brain injury	25 (11.2%) ^{a,b}	37 (26.1%) ^a	551 (63.5%)	< 0.001
Injury Severity Scale	10 (8–17) ^{a,b}	22 (13–29)	17 (9–29)	< 0.001
Injury Severity Scale				
< 15	161 (72.2%)	51 (35.4%)	360 (41.0%)	
15–30	55 (24.7%)	62 (43.1%)	351 (39.9%)	< 0.001
> 30	7 (3.1%)	31 (21.5%)	168 (19.1%)	
Other peri-intubation medications used	200 (88.5%) ^{a,b}	72 (49.0%) ^a	246 (27.7%)	< 0.001
In-hospital mortality	4 (1.8%)	25 (17.0%)	226 (25.5%)	< 0.001
Hypotension 24-h post-intubation	50 (22.6%)	43 (31.6%)	265 (31.7%)	0.03
Vasopressor requirement 24-h post-intubation	40 (18.4%)	45 (34.6%)	172 (21.2%)	0.001
Need for blood transfusion within 24 h	73 (33.8%) ^b	104 (73.2%) ^a	282 (32.4%)	< 0.001
Blood pressure				
Systolic				
Pre-intubation	125 (112–140) ^a	121 (102–142) ^a	138 (120–161)	< 0.001
First post-intubation	105.5 (92–124) ^{a,b}	120 (95–138.5) ^a	141 (118–164)	< 0.001
Second post-intubation	104 (90–120) ^{a,b}	114.5 (92–140) ^a	133 (115–156)	< 0.001
Third post-intubation	105 (92–124) ^a	108 (94–135) ^a	127 (109–148)	< 0.001
Diastolic				
Pre-intubation	71 (60–82) ^a	74 (59–91) ^a	87 (71–100)	< 0.001
First post-intubation	58 (50–70) ^{a,b}	70 (54–86) ^a	86 (70–100)	< 0.001
Second post-intubation	58 (50–65) ^{a,b}	64.5 (53–85) ^a	81 (65–94)	0.001
Third post-intubation	58 (50–65) ^{a,b}	65 (54–80) ^a	76 (62–89)	< 0.001
Heart rate				
Pre-intubation	92 (79–107) ^{a,b}	100 (85–115)	103 (85–122)	< 0.001
First post-intubation	98 (84–111) ^{a,b}	105 (90–121)	103 (82–120)	0.004
Second post-intubation	93 (80–104) ^b	100 (88–119) ^a	96 (79–115)	0.002
Third post-intubation	88.5 (78.5–98.5) ^{a,b}	98 (84–114.5)	94 (78–111)	< 0.001
Vasopressor within 15 min of intubation	35 (15.6%) ^a	26 (18.1%) ^a	51 (5.9%)	< 0.001
Complications	83 (36.7%)	92 (62.6%)	628 (70.7%)	< 0.001
Discharge disposition				
Home with/without services	143 (63.3%)	53 (36.1%)	281 (31.7%)	< 0.001
Other healthcare facility	65 (28.7%)	53 (36.0%)	309 (34.8%)	
Other	14 (6.2%)	14 (9.5%)	66 (7.4%)	

Table 2 (continued)

Characteristic	Induction agent			p-value
	Propofol (n = 226)	Ketamine (n = 147)	Etomidate (n = 887)	
Comorbidities				
Neurologic disorders	9 (4.0%)	1 (11.7%)	43 (4.9%)	0.06
Cardiovascular disorders	5 (2.2%)	2 (1.4%)	42 (4.7%)	0.052
Pulmonary disorders	4 (1.8%)	2 (1.4%)	10 (1.1%)	0.66
Diabetes	15 (6.6%)	8 (5.4%)	64 (7.2%)	0.72
HTN	19 (8.4%)	14 (9.5%)	106 (12.0%)	0.26
History of TIA/CVA	2 (0.9%)	2 (1.4%)	18 (2.0%)	0.59
History of vascular disease	0	0	1 (0.1%)	0.99
History of PE/DVT	2 (0.9%)	0	4 (0.5%)	0.42
None	53 (23.5%) ^a	32 (21.8%)	140 (15.8%)	0.011
Neurologic muscle blocker				
Succinylcholine	101 (44.7%)	89 (60.5%)	605 (68.2%)	
Rocuronium	106 (46.9%)	49 (33.3%)	255 (28.8%)	
Vecuronium	6 (2.7%)	0	21 (2.4%)	
Cisatracurium	2 (0.9%)	0	0	<0.001
Mivacurium	0	0	1 (0.1%)	
Other	0	0	2 (0.2%)	
None	11 (4.9%)	9 (6.1%)	3 (0.3%)	

Results are reported as no. (%) or median (IQR) as appropriate. The total *n* for this table excludes patients who received induction agents other than propofol, etomidate, or ketamine

CVA cerebrovascular accident, DVT deep vein thrombus, HTN hypertension, PE pulmonary embolism, TIA transient ischemic attack

^aSignificantly different from Etomidate group at a DCSF-adjusted or Bonferroni-adjusted $p < 0.05$ for continuous or categorical variables, respectively

^bSignificantly different from Ketamine group at a DCSF-adjusted or Bonferroni-adjusted $p < 0.05$ for continuous or categorical variables, respectively

propofol, induction with etomidate was significantly associated with higher complication rates (Table 5).

Significant differences in the complication rate per hospital stay were observed when comparing induction agent used. There were 832 (63.9%) patients who experienced a complication, and the median number of complications was one (Table 1). Compared to induction with propofol, patients induced with ketamine had a similar mean number of complications (IRR 1.3, 95% CI: 0.9, 1.8; $p = 0.18$), whereas patients induced with etomidate had a significantly higher mean number of complications (IRR 1.7, 95% CI 1.2, 2.5; $p = 0.008$). The estimated complication rate was 1.0, 1.3, and 1.7 per hospital stay for patients induced with propofol, ketamine, and etomidate, respectively (Table 5).

Comparison of outcomes in patients with ISS > 16

There were 644 patients with an ISS > 16. Patients who received ketamine and etomidate had an increased risk of mortality compared to propofol (Table 6). There was no difference among the three agents with respect to

hypotension or vasopressor use 24-h post-intubation or discharge disposition (Table 6). Patients receiving etomidate were at an increased risk of developing complications relative to propofol (Table 7).

Comparing RSIs performed in the ED to the OR

There were considerably greater RSIs performed in the ED ($n = 948$) compared to the OR ($n = 325$). Asleep direct laryngoscopy was most commonly used in both the ED (490, 55.4%) and the OR (184, 61.7%), followed by asleep video laryngoscopy (295, 33.4% and 69, 23.1%, respectively). In both the ED and OR, the provider most commonly performing the RSI was a resident. There was no difference in the first pass success rate in both ED and OR intubations. Patients intubated in the ED experienced a significantly higher in-hospital mortality and complication rate post-intubation, after adjusting for any confounding effects of hospital site (Table 3).

Table 3 Comparison of ED to OR intubations ($n = 1273$)

Variable	Intubation location no. (%)		<i>p</i> -value
	ED ($n = 948$)	OR ($n = 325$)	
Induction medication			
None	21 (2.2)	1 (0.3%)	< 0.001
Propofol	5 (0.5%)	219 (67.4%)	
Ketamine	68 (7.2%)	76 (23.4%)	
Etomidate	849 (89.6%)	15 (4.6%)	
Midazolam	1 (0.1%)	6 (1.9%)	
Fentanyl	3 (0.3%)	8 (2.5%)	
Other	1 (0.1%)	0	
Neuromuscular medication			
None	9 (1.0%)	14 (4.3%)	< 0.001
Succinylcholine	638 (67.3%)	167 (51.4%)	
Rocuronium	292 (30.8%)	135 (41.5%)	
Vecuronium	6 (0.6%)	6 (1.9%)	
Cisatracurium	0	2 (0.6%)	
Mivacurium	1 (0.1%)	0	
Other	2 (0.2%)	1 (0.3%)	
Specialty of provider			
ED	919 (96.9%)	2 (0.6%)	< 0.001
Anesthesiologist	1 (0.1%)	294 (90.5%)	
Surgeon	1 (0.1%)	1 (0.3%)	
Critical care specialist	0	6 (1.9%)	
Unknown/other	27 (2.9%)	22 (6.8%)	
Provider training			
Attending	67 (7.6%)	25 (8.2%)	< 0.001
Resident	598 (67.6%)	175 (57.6%)	
Fellow	1 (0.1%)	0	
CRNA	0	39 (12.8%)	
Student	1 (0.1%)	8 (2.6%)	
Unknown/other	218 (24.6%)	57 (18.8%)	
Intubating technique			
Asleep direct laryngoscopy	490 (55.4%)	184 (61.7%)	< 0.001
Asleep videolaryngoscopy	295 (33.4%)	69 (23.1%)	
Asleep LMA/supraglottic airway	0	2 (0.7%)	
Asleep fiberoptic	9 (1.0%)	8 (2.7%)	
Awake direct laryngoscopy	9 (1.0%)	0	
Awake videolaryngoscopy	3 (0.3%)	1 (0.3%)	
Awake fiberoptic	1 (0.1%)	1 (0.3%)	
Surgical airway	1 (0.1%)	14 (4.7%)	
Unknown/other	76 (8.6%)	19 (6.4%)	
DL blade			
Macintosh	412 (53.7%)	190 (69.1%)	< 0.001
Miller	10 (1.3%)	4 (1.5%)	
Other	3 (0.4%)	0	
Unknown	343 (44.7%)	81 (29.5%)	
Location of ETT			
Oral	848 (95.7%)	277 (93.5%)	< 0.001
Nasal	6 (0.7%)	1 (0.3%)	
Tracheal	2 (0.2%)	1 (0.3%)	
NS	30 (3.4%)	17 (5.7%)	

Table 3 (continued)

Variable	Intubation location no. (%)		<i>p</i> -value
	ED (<i>n</i> = 948)	OR (<i>n</i> = 325)	
Number of intubation attempts ^a	1 (1–1)	1 (1–1)	0.26
In-hospital mortality ^b	247 (26.1%)	18 (5.5%)	<0.001
Complication ^b	674 (71.1%)	131 (40.3%)	<0.001
Hypotension 24 h post intubation ^b	282 (31.6%)	84 (26.9%)	0.37
Vasopressor requirement 24 h post intubation ^b	187 (21.6%)	74 (24.1%)	0.94

Total *n* for Table 3 excludes patients who were intubated in locations other than the ED and OR

ED emergency department, OR operating room, CRNA certified registered nurse anesthetist, LMA laryngeal mask airway, NS not specified

^aMedian (IQR); *p*-value calculated by the Wilcoxon rank sum test

^b*p*-value calculated by the Cochran–Mantel–Haenszel test, adjusting for hospital site

Table 4 Patient outcomes by induction agent used (*n* = 1260)

Outcome	Induction agent			<i>p</i> -value
	Ketamine vs. etomidate	Ketamine vs. propofol	Etomidate vs. propofol	
In-hospital mortality	1.5 (0.7, 3.0)	3.2 (0.9, 11.9)	4.7 (1.2, 18.5)*	0.06
Hypotension 24 h post intubation	1.4 (0.8, 2.4)	1.2 (0.7, 2.2)	1.6 (0.8, 3.3)	0.36
Vasopressor requirement 24 h post intubation	0.8 (0.4, 1.4)	2.1 (1.1, 3.8)*	1.5 (0.7, 3.3)	0.07
Complication	1.0 (0.6, 1.8)	1.0 (0.6, 1.8)	1.3 (0.7, 2.7)	0.61
Discharged home with/without services	1.7 (0.9, 3.1)	0.9 (0.5, 1.7)	1.5 (0.7, 3.2)	0.22

Estimates represents OR (95% CI). All models are adjusted for hospital site, age, injury severity score (ISS), revised trauma score (RTS), traumatic brain injury (TBI), and intubation location

*Significantly different at a Bonferroni-adjusted *p* < 0.05

Discussion

There is no specific induction agent of choice for RSIs performed in trauma patients described in the literature or trauma or anesthesiology society guidelines. The few existing studies that examine induction agents used for trauma RSIs have small sample sizes and it is difficult to make definitive recommendations on the ideal induction agent from the reported findings. Additionally, there is a paucity of studies that compare the outcomes of various induction agents in trauma patients, and few that specifically compare propofol, ketamine and etomidate. To our knowledge, this is one of the largest studies evaluating induction medications used for RSIs in adult trauma patients at two US level I trauma centers, and the second study to compare outcomes among the three most commonly used agents, etomidate, propofol, and ketamine. This study identified the most commonly used induction agents and determined their outcomes on mortality, hospital LOS, ICU LOS, ventilator days, hemodynamics, and vasopressor requirement peri-intubation and at 24 h after intubation, and complications.

The most commonly used induction agents for RSI in trauma patients were etomidate, propofol, and ketamine.

Overall, the most commonly used agent was etomidate. Barbiturates, such as thiopental, have been used with decreasing frequency over time, and thiopental is not routinely available at many U.S. trauma centers. The hospitals included in this study do not routinely use barbiturates for trauma RSIs. When comparing RSIs performed in the ED to the OR, etomidate was most commonly used by ED providers, while propofol was most commonly in OR RSIs. This discrepancy may be due to the fact that a majority of the intubations were performed in the ED, and the provider preference was etomidate. A recent multicenter study performed by Leede et al. also reported that etomidate was the most commonly used agent (being used in 85% of patients) [13]. The most commonly used neuromuscular blocking agent was succinylcholine, followed by rocuronium in both ED and OR RSIs. Our finding that succinylcholine is the neuromuscular blocking agent of choice in RSIs is corroborated by the existing EAST guidelines for paralytic use for RSIs [2]. However, with the increased use and availability of sugammadex, an agent which quickly reverses the paralytic effects of rocuronium and vecuronium, rocuronium may be a reasonable alternative for RSIs.

Many studies report that etomidate is very commonly used as it was once recommended by the American College

Table 5 Patient outcomes by induction agent used (*n* = 1260)

Induction agent	IRR (95% CI)	<i>p</i> -value	Predicted LOS/complication rate (95% CI)
ICU LOS			
Propofol	Ref	Ref	12.5 (9.0–16.0)
Ketamine	0.9 (0.7–1.2)	0.49	11.3 (9.1–13.6)
Etomidate	0.8 (0.6–1.1)	0.25	10.5 (9.6–11.3)
Total hospital LOS			
Propofol	Ref	Ref	20.0 (15.1–25.0)
Ketamine	0.99 (0.8–1.3)	0.94	19.8 (16.0–23.6)
Etomidate	0.8 (0.6–1.1)	0.15	16.3 (14.9–17.6)
Days on MV			
Propofol	Ref	Ref	6.9 (4.8–9.0)
Ketamine	1.2 (0.9–1.6)	0.31	8.0 (6.3–9.7)
Etomidate	1.1 (0.8–1.5)	0.68	7.4 (6.8–8.0)
Number of complications			
Propofol	Ref	Ref	1.0 (0.7–1.4)
Ketamine	1.3 (0.9–1.8)	0.18	1.3 (1.0–1.6)
Etomidate	1.7 (1.2–2.5)	0.008	1.7 (1.6–1.9)

By negative binomial regression. All models are adjusted for hospital site, age, injury severity score (ISS), revised trauma score (RTS), traumatic brain injury (TBI), and induction location. The NB model for complications was offset by the total length of stay (LOS)

ICU intensive care unit, LOS length of stay, MV mechanical ventilation

of Surgeons Committee on Trauma’s Advanced Trauma Life Support [4, 5, 14, 15]. However, this study found that etomidate was associated with the highest in-hospital rate of complications and associated risk of mortality. The poor outcomes associated with etomidate could be due to the fact that it was the most frequently used agent in the ED, and patients requiring intubation in the ED were in a more critical state requiring emergent intervention, and already susceptible to poor outcomes. Although the etomidate group appeared to have more stable preinduction vital signs compared to ketamine and propofol, it also had patients who were the oldest,

had the lowest RTS, had the highest incidence of TBI, and had high ISS. Patients in the propofol group were younger, had a normal shock index, had the lowest number of TBI patients, and had less severe injuries (median ISS = 10). However, we controlled for many of these factors (age, ISS, RTS, TBI, intubation location, and hospital site) and still etomidate was associated with increased risk of mortality.

Similarly, Leede et al. reported a lower mortality with propofol compared to ketamine and etomidate when evaluating trauma patients undergoing RSI in the ED [13]. This observation may be because patients receiving propofol in both our and Leede et al.’s studies, were more hemodynamically stable. Additionally, our study used propofol exclusively in the OR, so patients who required intubation in the ED were more likely to be unstable. In contrast to these findings, several studies comparing trauma RSIs with etomidate versus other agents did not report a difference or increase in the mortality rates between groups [5, 16, 17]. One explanation for these findings is that all the other studies were performed in the ED only, where patients were more likely to be in critical condition, and thus, there would not be a statistically significant difference in mortality when comparing etomidate to other agents [5, 16, 17]. Additionally, in the studies by Banh and Hinkewich et al., the non-etomidate group induction medications varied (i.e., benzodiazepines, opioids, ketamine, etc. were used), and there was no one designated comparative induction agent, thus, confounding the results [5, 17]. Hinkewich et al. did demonstrate an increased mortality in the etomidate group; however, this association with 28-day mortality was not statistically significant [17]. Furthermore, Banh et al. compared a liberal-use etomidate group to a limited-use etomidate group, so etomidate was used in both comparison groups, making the results biased and more difficult to generalize [5]. Future multicenter prospective studies are needed to definitively determine whether etomidate or selection bias was the cause of increased mortality seen in this study, and to further explore the role of propofol in trauma RSIs and the beneficial effects on mortality.

Table 6 Patient outcomes by induction agent in patients with ISS > 16 (*n* = 664)

Outcome	Induction agent			<i>p</i> -value
	Ketamine vs. etomidate	Ketamine vs. propofol	Etomidate vs. propofol	
In-hospital mortality	1.6 (0.8, 3.1)	4.3 (1.1, 16.5)*	6.8 (1.8, 25.3)*	0.003
Hypotension 24 h post intubation	1.0 (0.5, 1.9)	0.8 (0.4, 1.7)	0.8 (0.4, 1.7)	0.78
Vasopressor requirement 24 h post intubation	0.5 (0.3, 0.9)*	1.7 (0.8, 3.9)	0.8 (0.4, 2.0)	0.067
Complication	1.6 (0.8, 3.2)	1.7 (0.8, 3.7)	2.8 (1.2, 6.4)*	0.056
Discharged home with/without services	1.3 (0.6, 2.7)	1.0 (0.4, 2.2)	1.2 (0.5, 3.0)	0.78

Estimates represents OR (95% CI). All models are adjusted for hospital site, age, revised trauma score (RTS), traumatic brain injury (TBI), and intubation location

*Significantly different at a Bonferroni-adjusted *p* < 0.05

Table 7 Patient outcomes by induction agent used in patients with ISS > 16 (*n* = 664)

Induction agent	IRR (95% CI)	<i>p</i> -value	Predicted LOS/ complication rate (95% CI)
ICU LOS			
Propofol	Ref	Ref	18.8 (11.7–25.8)
Ketamine	0.8 (0.6–1.2)	0.27	15.1 (11.4–18.9)
Etomidate	0.7 (0.4–1.0)	0.041	12.2 (11.1–13.4)
Total hospital LOS			
Propofol	Ref	Ref	36.0 (22.0–49.9)
Ketamine	0.7 (0.5–1.1)	0.11	26.2 (19.6–32.8)
Etomidate	0.5 (0.3–0.8)	0.003	18.8 (16.–20.7)
Days on MV			
Propofol	Ref	Ref	10.5 (6.0–15.0)
Ketamine	1.0 (0.6–1.5)	0.96	10.4 (7.6–13.1)
Etomidate	0.9 (0.5–1.4)	0.50	9.0 (8.1–9.8)
Number of complications			
Propofol	Ref	Ref	1.2 (0.7–1.8)
Ketamine	1.4 (0.9–2.3)	0.14	1.7 (1.2–2.2)
Etomidate	2.1 (1.2–3.4)	0.005	2.5 (2.2–2.9)

By negative binomial regression. All models are adjusted for hospital site, age, revised trauma score (RTS), traumatic brain injury (TBI), and induction location. The NB model for complications was offset by the total length of stay (LOS)

ICU intensive care unit, LOS length of stay, MV mechanical ventilation

Etomidate was associated with higher complication rates, while propofol was associated with superior outcomes. However, compared to propofol and ketamine, there was no statistically significant difference in the hospital and ICU LOS, or MV days. There are several studies that support our findings that etomidate may be associated with poor outcomes in trauma RSIs. In a study comparing blunt hypotensive adult trauma patients undergoing RSI with etomidate versus a benzodiazepine agent, the etomidate group was associated with developing ARDS and multiorgan dysfunction syndrome (MODS). The most severe subgroup receiving etomidate had increases in hospital and ICU LOS and MV days, but no difference in mortality [4]. However, Leede et al.'s study did not observe a difference in LOS among etomidate, propofol, and ketamine [13]. The decrease in cortisol levels caused by etomidate may result in increased neutrophil margination into tissues that could lead to ARDS and MODS [4]. It is possible that etomidate administration in trauma patients may cause adrenal suppression leading to adverse outcomes. A randomized controlled trial comparing trauma patients induced with etomidate to midazolam and fentanyl demonstrated decreased cortisol levels and decreased release of cortisol following a cosyntropin stimulation test in the etomidate group. Although there was no difference in mortality

between the two groups, there was an increase in hospital and ICU LOS, as well as MV days in the etomidate group [18]. However, three studies comparing etomidate to either ketamine or non-etomidate agents reported no statistically significant difference in ICU and hospital LOS or MV days [5, 16, 17].

Although peri-induction hemodynamics were more stable in the etomidate group, it was associated with a higher rate of hypotension at 24-h post-intubation, compared to propofol, and similar rates of hypotension 24-h post-intubation as ketamine. Ketamine and propofol had similar hemodynamic profiles peri-induction, and although there was a decrease in BP from pre-induction, there was no significant hypotension. Leede et al. also did not observe a significant difference in peri-intubation hemodynamics when comparing propofol, etomidate, and ketamine; however, they did not report on 24-h post-intubation hemodynamics or vasopressor use [13]. Similarly, Upchurch et al. performed a study on 968 patients comparing etomidate and ketamine and reported that the ketamine group was associated with more vasopressor days in the 28-day period following the trauma [16]. A study comparing etomidate and propofol in 76 trauma patients reported etomidate was associated with more increases in post-induction SBP, and propofol did not demonstrate a statistically significant hypotension [19]. Lyon et al. also reported that ketamine and etomidate had similar hemodynamic profiles but etomidate was associated with a post-induction hypertensive response [20]. Bahn et al. examined 1325 trauma patients who either received etomidate or a non-etomidate induction agent. This study demonstrated less peri-induction and 24-h post-induction hypotensive episodes in the etomidate group [5]. However, the study did not report the agents used in the non-etomidate group and their hemodynamic profiles [5]. Finally, Dietrich et al. compared induction with propofol and a non-propofol agent in 83 trauma patients and reported there was a higher incidence of 30-min post-intubation hypotension in the propofol group [21]. Our results differ to other studies in that etomidate and ketamine were associated with hypotension 24-h post-intubation. Possible explanations for our findings include that the patients receiving etomidate were more critically ill and may have been in hemorrhagic shock and hypotensive as a result of their injuries, or etomidate caused adrenergic suppression resulting in hypotension.

The outcomes and effects on hypotension may also be affected by patients who present with hemorrhagic shock and those who require massive transfusion protocols. These patients may be more susceptible to hemodynamic instability peri-intubation than patients who do not require blood products, and thus, the hypotension observed after intubation may, in fact, be due to the underlying hemorrhagic shock, rather than an effect of the induction medication administered for RSI. In our study, only 478 (37.6%)

patients received blood products within 24 h of admission, and it is unclear if these patients received 1 unit of blood or large quantities of blood and/or massive transfusion protocol. Additionally, we lacked data on patients who were in hemorrhagic shock, so it is difficult to determine if this could have contributed to peri-induction hypotension. As most of the intubations resulted in rather hemodynamically stable profiles, it is unlikely that hemorrhagic shock majorly contributed to peri-induction hypotension. Additional research on the hemodynamic effects of various induction medications used in patients in hemorrhagic shock and/or receiving massive transfusion protocol are warranted.

Limitations

Our study is limited by its retrospective design and selection bias. We only included data from two Level I trauma centers, and thus, the results may not be generalizable. Furthermore, there was a modest sample size; larger sampling may reduce the risk of a type II error. Some patients in need of definitive airways were not intubated in the field and only received care upon arrival to a trauma center. A delay in optimal care and airway establishment (i.e., increasing the risk of hypoxemia) may have been a large contributor to adverse patient outcomes, especially for those patients intubated in the ED upon arrival. The retrospective design also made our study susceptible to missing or incomplete data such as the cause of death and/or number and type of complications. Using an electronic medical record is subject to data entry errors and may have resulted in missed, underrepresented or misclassified data. There are differences in the physician practices and trauma care between the two hospitals which could have affected our results as well. Additionally, we did not employ a universal induction agent and dosage protocol, so the choice of the induction medication and dosage was per the discretion of the physician performing the intubation and subject to selection bias and confounding by indication.

The documentation of timing of medication administration to intubation was missing and pre- and post-intubation vital signs were not standardized and not properly recorded at the specific time intervals we wanted. Additionally, the hypotensive effects of the medications could have been tempered with fluid or blood product administration, which we were not able to extract from our records, leading to false assumption of a normotensive response. Furthermore, the hemodynamics and outcomes could have varied and been impacted in patients who were in hemorrhagic shock, as well as, in those who were receiving massive transfusion protocol. Unfortunately, we did not have access to data on patients who were in hemorrhagic shock or were receiving massive transfusions. Secondary

outcomes could have been affected by patients who had early mortality, as we included patients who died within 24 h of admission. These patients did not have the opportunity to develop certain outcomes, such as complications, and LOS data would have been impacted. Finally, confounding by indication bias is conceivable; although we adjusted for many indicators of severity, other unmeasured variables were not accounted for in our analysis.

In conclusion, this study demonstrated that etomidate was associated with the highest rate and risk of mortality and complications. These findings cannot be generalized as the study was performed at two level I trauma centers and there are several confounding factors that could influence the results, one of them being that patients receiving etomidate were sicker to begin with, and expectedly, would have worse outcomes. A prospective, randomized controlled multicenter trial is required to better understand the effects of different induction agents on hemodynamics and outcomes and to establish standard of care guidelines.

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Availability of data and material The datasets used in this study are not publicly available because of patient confidentiality but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review boards of the Keck School of Medicine of the University of Southern California and the University of California, Irvine; and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Not applicable.

Consent for publication All authors have seen and approved the final manuscript and have given their consent for publication.

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