A multicenter investigation of the hemodynamic effects of induction agents for trauma rapid sequence intubation

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BACKGROUND: Several options exist for induction agents during rapid sequence intubation (RSI) in trauma patients, including etomidate, ketamine, and propofol. These drugs have reported variable hemodynamic effects (hypotension with propofol and sympathomimetic effects with ketamine) that could affect trauma resuscitations. The purpose of this study was to compare the hemodynamic effects of these three induction agents during emergency department RSI in adult trauma. We hypothesized that these drugs would display a differing hemodynamic profile during RSI.

METHODS: We performed a retrospective (2014–2019), multicenter trial of adult (≥18 years) trauma patients admitted to eight ACS-verified Level I trauma centers who underwent emergency department RSI. Variables collected included systolic blood pressure (SBP) and pulse before and after RSI. The primary outcomes were change in heart rate and SBP before and after RSI.

RESULTS: There were 2,092 patients who met criteria, 85% received etomidate (E), 8% ketamine (K), and 7% propofol (P). Before RSI, the ketamine group had a lower SBP (E, 135 vs. K, 125 vs. P, 135 mm Hg, $p = 0.04$) but there was no difference in pulse (E, 104 vs. K, 107 vs. P, 105 bpm, $p = 0.45$). After RSI, there were no differences in SBP (E, 135 vs. K, 130 vs. P, 133 mm Hg, $p = 0.34$) or pulse (E, 106 vs. K, 110 vs. P, 104 bpm, $p = 0.08$). There was no difference in the average change of SBP (E, 0.2 vs. K, 5.2 vs. P, −1.8 mm Hg, $p = 0.4$) or pulse (E, 1.7 vs. K, 3.5 bpm vs. P, −0.96, $p = 0.24$) during RSI.

CONCLUSION: Contrary to our hypothesis, there was no difference in the hemodynamic effect for etomidate versus ketamine versus propofol during RSI in trauma patients. (*J Trauma Acute Care Surg.* 2021;90: 1009–1013. Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, Level IV.

KEY WORDS: Rapid sequence intubation; induction agents; trauma; mortality; emergency.

The airway is usually the first priority in the evaluation and management of a trauma patient in the emergency department. This assessment often determines the need for a definitive airway, most commonly secured by rapid sequence intubation (RSI), the criterion standard for emergent endotracheal intubation. Despite its procedural standardization, there is no established best drug regimen for RSI in trauma. Several options exist for induction agents during RSI in trauma patients, including etomidate, ketamine, and propofol. These drugs have reported variable hemodynamic effects (hypotension with propofol and sympathomimetic effects with ketamine) that could affect trauma resuscitations.[1–3] Additionally, controversial reports surrounding the traditionally most hemodynamically favorable drugs, adrenal insufficiency with etomidate and increased intracranial pressure with ketamine, complicate the picture despite neither claim having been substantiated as effecting trauma patient outcomes.[4,5]

Published research on RSI focuses largely on immediate hemodynamic effects and intubation success, but trauma patients are rarely studied specifically.[6] Studies generally investigate "critically ill patients," which may include trauma patients but lump them with distinctly different populations such as severe sepsis patients. To our knowledge, there is no multicenter research into outcomes following the commonly used RSI drug regimens in adult trauma patients. The purpose of this study was to compare the hemodynamic effects of the three most common induction agents (etomidate, ketamine, and propofol) during emergency department RSI in adult trauma patients. We hypothesized that these drugs would display a differing hemodynamic profile during RSI.

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PATIENTS AND METHODS

We performed a retrospective (2014–2019), multicenter study of adult (≥18 years old) trauma patients admitted to eight ACS-verified Level I trauma centers (Fig. 1) who underwent emergency department RSI. Patients were identified through each site's trauma registry and subsequent chart review. Variables collected included demographics, mechanism of injury, prehospital and admission physiology, Injury Severity Score (ISS), medications given for RSI, systolic blood pressure (SBP), and pulse immediately before and after RSI. Patients were grouped based on which induction agent they received during RSI. If patients were intubated prior to arrival, received no induction agent, or received more than one induction agent, they were excluded from the study. The primary outcomes were change in heart rate and SBP before and after RSI, whereas the secondary outcomes were mortality, length of stay, and discharge disposition.

Data were analyzed using SAS (version 9.4) statistical software by using analysis of variance for the continuous variables and χ^2 for categorical variables. Values are reported as means and standard deviation or as a raw percentage. Differences were considered statistically significant at p less than 0.05. Variables that were significantly different between groups in bivariate analysis were then included in mixed effects modeling, with a random intercept for each participating center, to identify variables independently associated with a change in heart rate and/or SBP. Administration of etomidate (the most common agent) was used as the reference category for the models. The local institutional review boards at each participating site approved this study.

RESULTS

There were 2,092 patients who met criteria, 1,786 (85%) received etomidate (E), 169 (8%) ketamine (K), and 137 (7%)

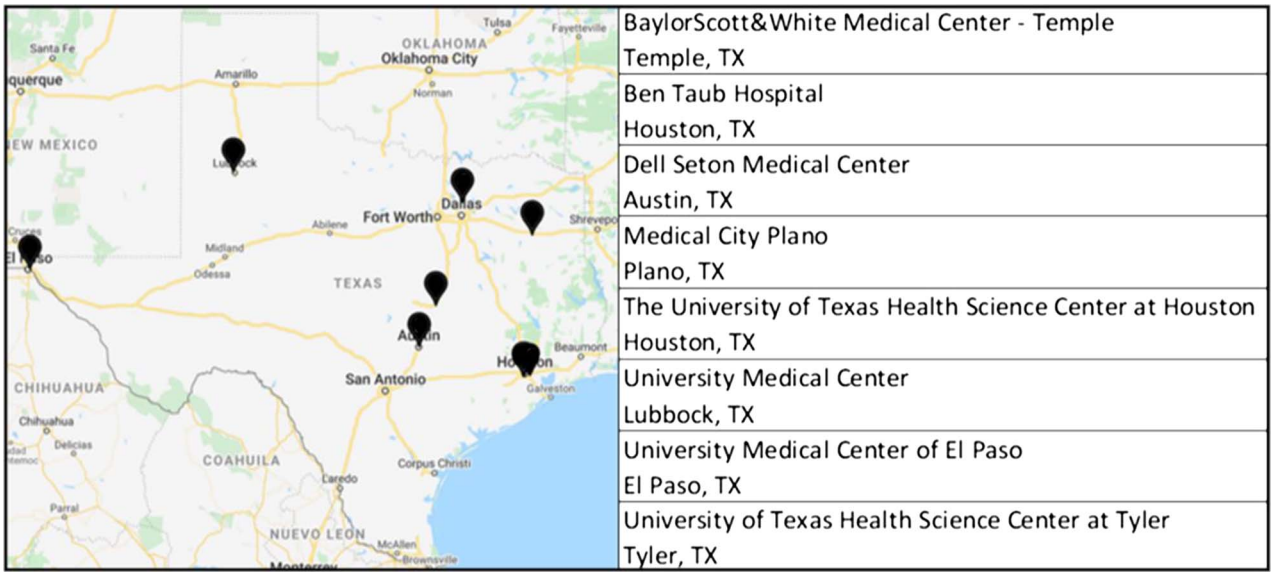

Figure 1. Participating Level I trauma centers: pictorial representation of contributing Level I trauma centers across Texas.

propofol (P). The etomidate group was older (E, 43 vs. K, 40 vs. P, 41 years; $p = 0.045$), less men (E, 78% vs. K, 80% vs. P, 88%; $p = 0.02$), more White (E, 60% vs. K, 54% vs. P, 29%, $p < 0.001$), and more often bluntly injured (E, 84% vs. K, 76% vs. P, 78%; $p = 0.009$). The propofol group was less often hypotensive (SBP <90 mm Hg) at presentation (E, 11% vs. K, 19% vs. P, 6%) and more often severely head injured (Glasgow Coma Score ≤ 8) (E, 46% vs. K, 40% vs. P, 56%; $p = 0.01$). There was no difference in ISS (E, 21 vs. K, 22 vs. P, 19; $p = 0.07$). These demographics are shown in Table 1.

Hemodynamics are shown in Table 2. Before RSI, the ketamine group had a lower SBP (E, 135 vs. K, 125 vs. P, 135 mm Hg; $p = 0.04$) but there was no difference in pulse. After RSI, there were no differences in SBP or pulse, and there was no difference in the average change of SBP or pulse during RSI.

On analysis of secondary outcomes, there was no difference in intensive care unit (ICU) length of stay (E, 8 vs. K, 8 vs. P, 9 days; $p = 0.69$) nor hospital length of stay (E, 14 vs. K, 14 vs. P, 15 days; $p = 0.93$). Propofol was associated with more discharges home (E, 45% vs. K, 44% vs. P, 56%; $p = 0.05$) and lower mortality (E, 18% vs. K, 23% vs. P, 10%, $p = 0.01$). In the mixed effect modeling, including a random intercept for each center, there was no significant association between the induction agent and change in heart rate nor change in SBP. Additionally, including each center as a fixed effect had no bearing on the results.

DISCUSSION

Based on the current literature, we hypothesized that propofol, etomidate, and ketamine would display a differing hemodynamic profile during RSI. Contrary to our hypothesis, there was no difference in the hemodynamic effect for etomidate versus ketamine versus propofol during RSI in trauma patients, suggesting that this population is a distinct patient subset and does not show the same hemodynamic change as other studied populations (such as "critically ill patients") during RSI in the emergency department. On analysis of patient centered outcomes, there was no difference in hospital or ICU length of stay; however, propofol was associated with decreased mortality compared with etomidate and ketamine.

Etomidate has been shown to create adrenal insufficiency and there are concerns for ketamine's sympathomimetic activity; however, the literature has failed to substantiate a difference between ketamine and etomidate in adult trauma patients. In 2009, Jabre et al.[7] compared outcomes following etomidate and ketamine for critically ill patients, with a trauma subset, and found

TABLE 1. Demographics

	Etomidate, n = 1786	Ketamine, n = 169	Propofol, n = 137	*p*
Age, y	43 ± 18	40 ± 17	41 ± 16	0.045*
Male	78	80	88	0.02*
White	60	54	29	<0.0001*
Blunt injury	84	76	78	0.009*
Prehospital hypotension (<90 mm Hg SBP)	11	19	6	0.002*
Low GCS score (<8)	46	40	56	0.01*
ISS	21 ± 14	22 ± 16	19 ± 12	0.07

* indicates statistical significance. GCS, Glasgow Coma Score.

TABLE 2. Hemodynamic During RSI

	Etomidate, n = 1786	Ketamine, n = 169	Propofol, n = 137	*p*
Pre-RSI				
SBP, mm Hg	135 ± 50	125 ± 37	135 ± 34	0.04*
Pulse, bpm	104 ± 28	107 ± 26	105 ± 30	0.45
Post-RSI				
SBP, mm Hg	135 ± 36	130 ± 40	133 ± 34	0.34
Pulse, bpm	106 ± 26	110 ± 27	104 ± 27	0.08
Change during RSI				
SBP, mm Hg	0.2 ± 50	5.2 ± 32.3	−1.8 ± 32	0.4
Pulse, bpm	1.7 ± 22.6	3.5 ± 25.3	−1.0 ± 23	0.24

* indicates statistical significance.

no difference in mortality nor length of stay associated with either drug. They also found no difference in the change in SBP, diastolic blood pressure, and oxygenation (SpO_2). This is corroborated by Upchurch et al.[5] in their retrospective study of an institutional switch to ketamine from etomidate as standard for RSI in trauma. This study found no difference in outcomes, including mortality and length of stay, between patients who received etomidate and ketamine. They did not analyze change in hemodynamics. The results of these studies align with our findings of no difference in hemodynamics, length of stay, and mortality between ketamine versus etomidate use during RSI of trauma patients.

A recent retrospective study in pediatric trauma found propofol use to be associated with worsening hypotension compared with etomidate, ketamine, and midazolam.[8] Dietrich et al.[2] found that propofol increased the odds of postintubation hypotension 3.64 times compared with other nonpropofol induction agents (etomidate and midazolam) during RSI in trauma. Neither study found a statistically significant difference in mortality nor length of stay. Contrasting these studies, a 2015 retrospective study by Zettervall et al.[9] analyzed 76 adult trauma patients (the majority of whom were hemodynamically stable at presentation) and found that reduced dose propofol did not result in post-RSI hypotension. This study also failed to find a mortality difference between propofol and etomidate. Our results align with the third study. There was no difference in the change of hemodynamics during RSI for trauma patients treated with propofol, ketamine, or etomidate. It should be noted that there were fewer hypotensive patients in the propofol group (E, 11% vs. K, 16% vs. P, 6%; $p = 0.002$), similar to Zettervall's patient population. There are several explanations for this difference in hemodynamic outcomes between studies. First, Johnson et al.[10] found that swine in hemorrhagic shock showed exaggerated hypotension with propofol, likely due to decreased clearance. It is possible that by avoiding the use of propofol in hypotensive patients, we selected for patients who would not have a significant drop in SBP. Second, this study did not collect propofol dosage but, it is possible that the dosing physician accounted for hemodynamic profile during RSI. If the physicians used lower propofol dosages, then there would be low risk of hypotension as shown by Zettervall et al.

The literature has not reported a mortality benefit with propofol use. Here, we show that propofol is associated with decreased mortality. This could represent a true association or there is another unaccounted-for factor influencing mortality not uncovered in the regression. As discussed, there were fewer hypotensive patients in the propofol group, it is possible that in this nonhypotensive subset of patients, propofol has a mortality benefit versus etomidate and ketamine. Regardless of the cause, this study shows that propofol continues to remain a commonly used induction agent in trauma patient emergency room RSI and there should be further prospective investigation into the mortality benefit and hemodynamics of propofol compared with other popular induction agents.

To our knowledge, this study is the largest study of emergency room RSI induction agents for trauma patients and the only multicenter study of its kind. As postintubation hypotension has been associated with increased rate of adverse events in trauma patients, it is of clinical importance to know what medications increase the risk of hypotension during RSI.[11] Here, we show that the three most common induction agents are etomidate, ketamine, and propofol and that all three of these medications produce a similar hemodynamic profile in trauma patients. Furthermore, our data show an association between propofol and decreased mortality that requires more clinical study but, if substantiated, this finding could change trauma RSI practice.

Because this was a retrospective study, we were not able to control the size of each group and the sizes differed significantly, with 85% of patients receiving etomidate. Despite the skewed group distribution, a post hoc power analysis revealed that 175 subjects per group would provide 80% power to detect a clinically relevant 15 mm Hg difference in change in SBP, and 99 subjects per group would provide 80% power to detect a clinically relevant 10 bpm difference in change in heart rate. The differences in blood pressures were never greater than 10 mm Hg in our study; thus, we can be confident in our failure to reject the null hypothesis. In addition, even if this study committed a type II error, it is unlikely that a 5 mm Hg change in SBP and 4 bpm change in pulse would be clinically significant.

There are several limitations to this study. This study is a retrospective study and is thus subject to the biases and weaknesses of its data. Data were collected from site trauma registries and supplemented with chart review. There is room for human error in each of these steps and incomplete, misinterpreted, or erroneous data in the chart. By being retrospective, this study cannot conclude a causal relationship and is limited to associations. Further research into the hemodynamics of these common drugs in a prospective manner is warranted and supported by our retrospective research showing no difference in the hemodynamics of etomidate, ketamine, and propofol. Additional research into the mortality benefit or other influential factors is needed to further clarify the effect of propofol on the trauma patients.

The literature surrounding emergency department RSI induction agents rarely examines trauma patients as their own population. This study contributes to the ongoing literature by having the largest subject number (n = 2,092) and being the only multicenter study of trauma-specific RSI induction agents. There was no difference in the hemodynamic effect for etomidate versus ketamine versus propofol during RSI in trauma patients. This finding obviates hemodynamic change as an influential factor when choosing an induction agent for trauma RSI. Looking at other factors that could affect induction agent choice, there was no difference in hospital or ICU length of stay; however, there was a mortality

benefit associated with propofol use. This study demonstrates that it would be reasonable to consider etomidate, ketamine, or propofol as an induction agent for trauma RSI.

AUTHORSHIP

E.L., C.V.R.B., J.K., C.W., A.J.R.T., A.C., E.F., J.R., R.R., M.C., Texas Trauma Study Group participated in the study conception and design. E.L., C.V.R.B., J.K., C.W., A.J.R.T., A.C., E.F., J.R., R.R., M.C., Texas Trauma Study Group participated in the acquisition of data. E.L., C.V.R.B., J.K. participated in the analysis and interpretation of data. E.L., C.V.R.B., J.K. E.L., C.V.R.B., J.K., C.W., A.J.R.T., A.C., E.F., J.R., R.R., M.C., Texas Trauma Study Group participated in the drafting of the article. Participated in the critical revision.

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DISCLOSURE

The authors declare no funding or conflict of interest.

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