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ORIGINAL ARTICLE

Use of propofol as an induction agent in the acutely injured patient

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Abstract
Purpose Etomidate is a commonly used agent for rapid sequence induction (RSI) in trauma due to its limited hemodynamic effects. Given a recent nationwide shortage of etomidate, alternative induction agents may be required. Propofol is a frequent substitute; however, concern exists regarding its potential hypotensive effects. The study attempts to determine the hemodynamic effects of propofol and etomidate following RSI in trauma bay.
Methods A retrospective study was performed on 76 consecutive trauma patients requiring RSI at a single academic medical center. Patients were stratified by age, gender, mechanism of injury, Injury Severity Score (ISS), and Glasgow Coma Scale (GCS). Pre-induction and post-induction hemodynamic parameters were evaluated, and a multivariate regression analysis was performed.
Results The mean age was 42, ISS was 13, and GCS was 9.8. The mean dose of propofol was 127 ± 5 mg and the mean dose of etomidate was 21 ± 6 mg. Patients who received propofol were younger and had a lower ISS. The etomidate group had significantly increased post-induction systolic blood pressure but no difference in mean arterial pressure or heart rate when compared to pre-induction parameters. The propofol group had no significant changes in any post-induction parameter compared to pre-induction parameter.
Conclusion RSI with propofol did not result in hypotension in our patient population, suggesting that a reduced dose of propofol may represent a reasonable alternative to etomidate in hemodynamically stable trauma patient. Further research is warranted to assess the safety of propofol in the acutely injured patient.

Keywords Trauma · Rapid sequence induction · Propofol · Etomidate · Intubation

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Introduction

Rapid sequence induction (RSI) is an intubation technique utilized to expedite the endotracheal intubation in patients at high risk for aspiration. The purpose of this technique is to minimize the time period between loss of a protected airway and placement of a cuffed endotracheal tube. First described in 1970, this technique traditionally involves pre-oxygenation, administration of a rapid onset sedating medication, injection of a neuromuscular blocking agent (i.e., succinylcholine) followed by endotracheal intubation without the use of positive pressure ventilation [1]. This technique was initially introduced to address concerns that aspiration might be perpetuated by positive pressure ventilation in patients with full stomach and has become the most commonly used technique for emergent intubation [2, 3]. While the impact of RSI on aspiration risk is controversial, a full body of literature does show that this practice can be done with higher rates of successful intubation than traditional practices and with fewer complications in

appropriately selected patients [4–8]. Currently, RSI is the recommended technique for intubation in critically injured patients [9].

Despite the widespread use of RSI for patients at risk for aspiration, there is significant variation in the execution of this technique including the choice of induction agent. For patients requiring this anesthetic technique, the ideal drug provides rapid onset of action to maximize intubation conditions including minimal response to laryngeal stimulation, minimal hemodynamic changes, and adequate paralysis. Given that this ideal drug does not currently exist, agent availability and anesthesiologist preference are the guiding factors in induction agent selection. Multiple drugs are available for induction including etomidate, ketamine, and propofol with etomidate being the most widely used [10].

Beginning in 2011, our hospital experienced the impact of the Food and Drug Administration declared nationwide shortage of etomidate which required the utilization of other agents for induction [11]. Because of its widespread use and comfort among anesthesiologists, the decision was made to utilize propofol as the first-line induction agent for critically injured patients when etomidate was unavailable. Given the documented side effects of both propofol and etomidate, we elected to utilize this change in practice to evaluate the effects of these medications. Therefore, we sought to determine the hemodynamic impact of RSI using either etomidate or propofol in critically injured patients.

Materials and methods

A retrospective study of 76 consecutive critically injured patients requiring emergent intubation in the trauma bay at a single academic medical center was performed from October 2011 to September 2012. Patients were initially identified through the hospital trauma center registry and were excluded if they were under 16 years of age, arrived intubated, were intubated in the trauma bay without the use of induction agents, received vasopressor prior to intubation, or lacked documentation of pre- and post-induction hemodynamic parameters. Data were collected from the trauma flow sheet and patients were stratified by age, gender, admission Glasgow Coma Scale (GCS), Injury Severity Score (ISS), mechanism of injury, and indication of intubation. The study cohort was divided into two groups based on the type of induction agent used. The date of patient's arrival determined the induction agent used. Prior to May 2012, when the shortage was announced, induction agent was guided by anesthesiologist preference. After May 2012, all patients received propofol due to limited availability of etomidate. Dosing of propofol and etomidate was ultimately determined by the attending anesthesiologist with guidance from posted trauma bay recommendations. Succinylcholine was solely utilized for neuromuscular blockade. The use of lidocaine, midazolam, lorazepam, vecuronium, and fentanyl was documented. All intubations were completed using RSI and were performed by anesthesia and emergency medicine senior residents under the guidance of an attending anesthesiologist. Hemodynamic parameters including mean arterial pressure (MAP), systolic blood pressure (SBP), and heart rate (HR) were collected immediately pre-induction and on average 3 min post-induction. The need for vasopressor medication following intubation was also documented.

Statistical analysis

Discrete variables were compared using Fischer Exact Test. For continuous variables, QQ plots and histograms were examined to ensure normal distributions. Means were compared across treatment groups using two-tailed Student's t test to account for unequal variance. Univariate analysis within groups across time periods was performed with paired t test to determine differences in pre- and post-induction hemodynamic parameters (Table 1). Multivariate generalized estimating equation models were utilized to correct for differences in age, Injury Severity Score, and pre-treatment hemodynamic variables, and to compare changes between treatment groups. SAS statistical software (version 9.2; Cary, NC) was used for analysis, and G-power3 was used for post hoc power analysis. Differences were considered significant when $p < 0.05$. This study was approved by the institutional review board at The George Washington University School of Medicine and Health Sciences, Washington, DC.

Results

Patient demographics

76 patients were evaluated with a mean age of 42 ± 19, a mean ISS of 13 ± 11, a mean admission GCS of 9.8 ± 4, 76 % were male and 92 % sustained blunt injury. Traumatic brain injury (TBI) was diagnosed in 30 % of the study cohort (Table 2). The most common indications for intubation were altered mental status (61 %) followed by agitation (25 %) and respiratory distress (8 %) (Table 3). The study cohort consisted of patients receiving either propofol ($n = 57$, 75 %) or etomidate ($n = 19$, 25 %) as the induction agent for RSI. Patients receiving propofol were significantly younger (38 ± 16 vs. 53 ± 22, $P < 0.001$) and were less severely injured (ISS 11 ± 19 vs. 19 ± 13, $p < 0.02$) when compared to patients receiving etomidate. These differences were accounted for using a multivariate regression model in further analysis of hemodynamic outcomes. There were

no significant differences noted between the groups with respect to admission GCS, TBI, gender, mechanism of injury or indication for intubation (Tables 2, 3). The mean dose of propofol was 127 ± 5 mg and the mean dose of etomidate was 21 ± 6 mg. Succinylcholine was administered once in all the patients with dose of 100 mg. Phenylephrine was required in both groups (etomidate 5 % and propofol 7 %). There was no significant difference between the groups with respect to phenylephrine, lidocaine, midazolam, lorazepam, vecuronium, and fentanyl use or total dose required. There were no other alpha agonist agents used to support the BP as part of RSI. Conventional laryngoscopy was used in 90 % of intubations and 10 % were performed under the guides of the fiberoptic laryngoscopy. The mortality rate was 7.9 % and there was no significant difference in mortality between the propofol group and the etomidate group.

Hemodynamic outcomes

The changes in hemodynamic parameters before and after induction were evaluated within each study group using a multivariate analysis to account for demographic differences between groups, including age and Injury Severity Scores (Figs. 1, 2, 3). Following this analysis, the post-induction MAP, SBP and HR in the propofol group did not significantly change when compared to the pre-induction MAP, SBP, HR (MAP 95 (95 % CI 90–100) vs. 94 (95 % CI 89–99), $p = 0.57$; SBP 131 (95 % CI 125–138) vs. 131 (95 % CI 124–138), $p = 0.87$; HR 98 (95 % CI 90–106) vs. 101 (95 % CI 94–108), $p = 0.17$). Similarly, the post-induction MAP and HR in the etomidate group did not significantly change when compared to the pre-induction MAP and HR. (MAP 101 (95 % CI 89–114) vs. 106 (95 % CI 94–118), $p = 0.26$; HR 98 (95 % CI 86–109) vs. 92 (95 % CI 80–103), $p = 0.11$). The only statistically significant hemodynamic shift was found in the etomidate group where an increase in SBP was identified following induction (SBP 139 (95 % CI 119–158) vs.152 (95 % CI 133–171), $p = 0.02$, Table 4).

Discussion

Propofol is a highly lipid soluble alkylphenol which functions by acting on the GABA receptors inhibiting acetylcholine release from the hippocampus and prefrontal cortex. Currently, propofol is the most widely used induction agent for its beneficial effects on analgesia, sedation, and intubation [12]. Several studies demonstrate that the superior depression of laryngeal and pharyngeal reflexes achieved by propofol lead to more successful intubation when compared with etomidate. This is most likely due to

Table 1 Univariate analysis of hemodynamic outcomes

Drug	MAP pre-drug	MAP post-drug	*P* value
Propofol	98 ± 17	95 ± 17	0.35
Etomidate	105 ± 27	108 ± 29	0.28
Drug	SBP pre-drug	SBP post-drug	*P* value
Propofol	136 ± 22	134 ± 21	0.66
Etomidate	143 ± 41	156 ± 45	0.03
Drug	HR pre-drug	HR post-drug	*P* value
Propofol	96 ± 24	98 ± 24	0.12
Etomidate	104 ± 27	98 ± 19	0.14

Data expressed as mean (SD)

Paired *t* test

MAP mean arterial pressure, *SBP* systolic blood pressure, *HR* heart rate

Table 2 Patient demographics

Variable	Total *N*	Number or percentage	Propofol ($N = 57$)	Etomidate ($N = 19$)	*P* value
Age (years)	76	42 (±19)	38 (±16)	53 (±21)	0.0003*
Injury Severity Score	76	13 (±11)	11 (±10)	18 (±13)	0.02*
Admission Glasgow Coma Scale	76	9.8 (±4)	10 (±4)	9 (±45)	0.23*
Traumatic brain injury (%)	23	30 %	14 (25 %)	9 (47 %)	0.08
Blunt injury (%)	70	92 %	54 (95 %)	16 (84 %)	0.16**
Gender (% male)	58	76 %	43 (75 %)	15 (79 %)	0.99**
Mortality (%)	6	8 %	3 (5 %)	3 (16 %)	0.16**

Age, Injury Severity Score and Admission Glasgow Coma Scale data are expressed as mean (±standard deviation)

* Age, Injury Severity Score and Admission Glasgow Coma Scale: Student's *t* test

** Blunt injury, gender, and mortality: Fischer exact test

Table 3 Indication for intubation

Variable	Propofol ($n = 57$)	Etomidate ($n = 19$)	*P* value
Altered mental status	35 (61 %)	11 (58 %)	0.80
Combative	13 (23 %)	6 (32 %)	0.54
Respiratory distress	4 (7 %)	2 (11 %)	0.64
Other	3 (5 %)	0 (0 %)	0.57

P value: Fischer exact test

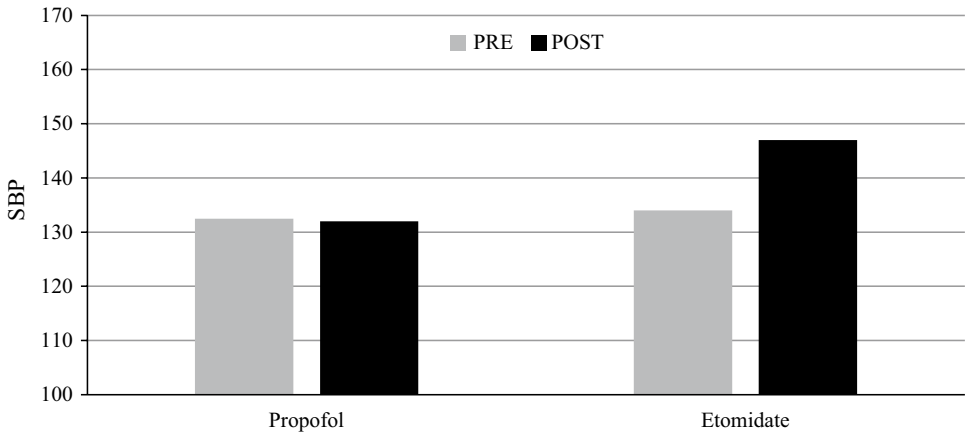

Fig. 1 Mean change in systolic blood pressure (SBP) corrected for age, Injury Severity Score, and gender

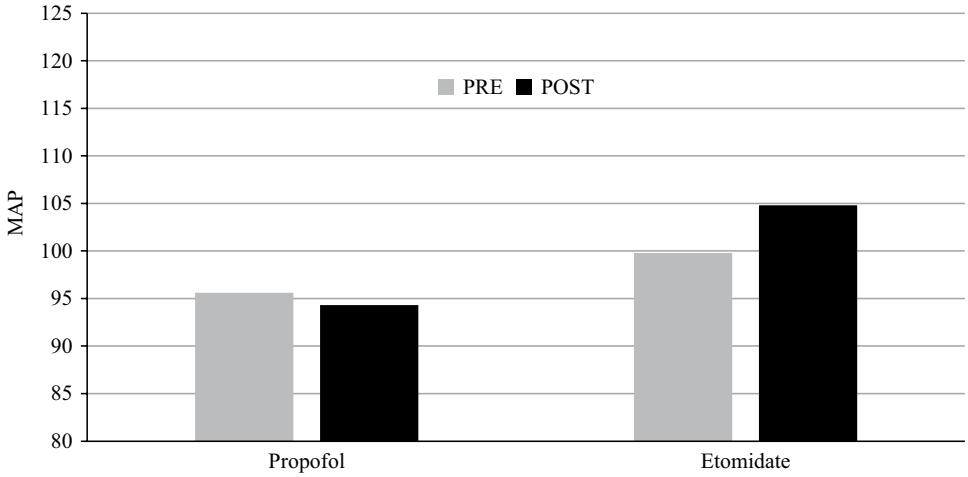

Fig. 2 Mean change in mean arterial blood pressure (MAP) corrected for age, Injury Severity Score, and gender

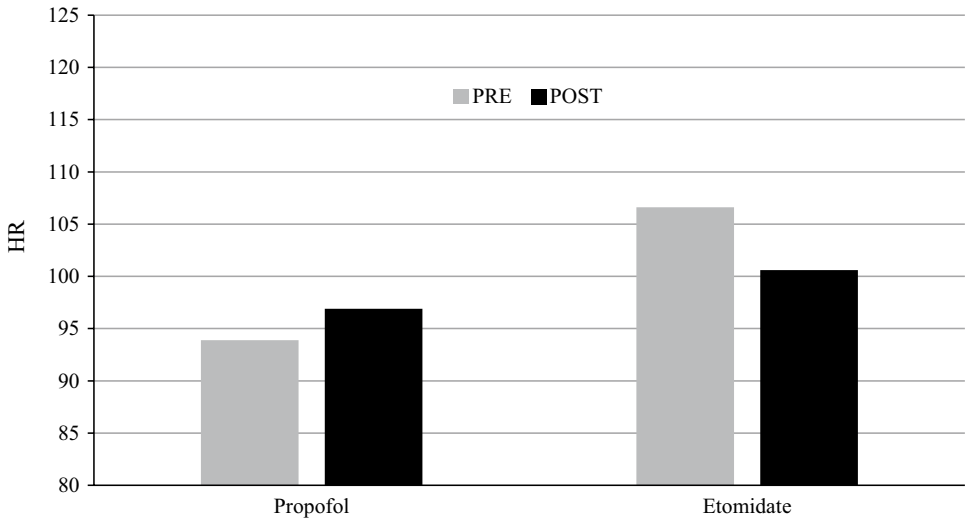

Fig. 3 Mean change in heart rate (HR) corrected for age, Injury Severity Score, and gender

suppression of cough and laryngospasm that is not seen to the same degree with etomidate [9, 13]. Traditionally, the major disadvantage to propofol has been the impact on hemodynamics with drops in systolic blood pressure noted to be as high as 20 mmHg following induction [14]. These hypotensive effects are thought to be due to a decrease in systemic vascular resistance and loss of sympathetic tone [12, 15]. While this side effect can often be tolerated

Table 4 Multivariate adjusted means for hemodynamic outcomes

Drug	MAP pre-drug	MAP post-drug	*P*-value
Propofol	95 (90–100)	94 (89–99)	0.57
Etomidate	101 (89–114)	106 (94–118)	0.26
Drug	SBP pre-drug	SBP post-drug	*P*-value
Propofol	131 (125–138)	131 (124–138)	0.87
Etomidate	139 (119–158)	152 (133–171)	0.02
Drug	HR pre-drug	HR post-drug	*P*-value
Propofol	98 (90–106)	101 (94–108)	0.17
Etomidate	98 (86–109)	92 (80–103)	0.11

Data expressed as adjusted mean (95 % Confidence Interval) by time

Z test from the generalized estimating equation

MAP mean arterial pressure, *SBP* systolic blood pressure, *HR* heart rate

among hemodynamically stable and euvolemic patients in the controlled setting of the operating room, patients with hypovolemia are potentially at risk for cardiovascular collapse as a result of induction with propofol. Furthermore, Jonson et al. found the hemodynamic effect of the propofol to be exaggerated in animals with hemorrhagic shock, likely due to decreased clearance and increased end-organ sensitivity [16]. For this reason, propofol has traditionally been avoided as the induction agent in hypotensive patients or those with clinical suspicion of hypovolemia.

Etomidate is an imidazole derivative which also functions through its impact on GABA receptors, although the full pharmacologic mechanism still remains unclear [12]. Etomidate is regarded in many trauma centers and emergency departments as the drug of choice for rapid sequence induction due to its consistent ability to successfully sedate without major shifts in patient hemodynamics even in hemodynamically unstable patients [17]. However, this practice has recently come under scrutiny due to etomidate's impact on adrenal suppression. Pandey et al. [7] found a 50 % reduction in serum cortisol levels following etomidate administration in patients undergoing coronary artery bypass grafting, although cortisol levels returned to baseline rates within 24 h. Today, a growing body of literature has found similar problems with the administration of etomidate in trauma patients, likely due to the disturbance of the hypothalamic–pituitary–adrenal axis as a result of trauma. In a recent study by Cotton et al. [18–20], the authors documented etomidate to be the only modifiable risk factor for the development of adrenal insufficiency in the acutely injured patient. In addition, several other studies have identified increased rates of adrenal suppression, ARDS, multiple organ dysfunction, and overall mortality in the trauma population due to the administration of etomidate.

To date, few studies provide comparison of etomidate and propofol within the trauma population. In a recent study by Hildreth et al. the authors argue against the use of etomidate due to increased mortality and organ dysfunction following even a single dose in the trauma patient, and the authors directly recommend against the utilization of etomidate [21]. Additional studies have also recommended alternatives to etomidate in the trauma population, suggesting that propofol be utilized as the agent of choice for all non-hypotensive trauma inductions [17, 20, 22]. However, more recently, multiple large studies in critical care, emergency medicine, and anesthesiology have found no difference in mortality among patients receiving etomidate compared to alternative induction agents [23–25]. Further research in this field is warranted to definitively answer this question.

This study found that propofol does not lead to significant hemodynamic changes when administered for rapid sequence induction in the trauma bay. Moreover, etomidate also has minimal effects on hemodynamics with only an increase in systolic blood pressure following administration. Neither etomidate nor propofol led to a significant post-induction reduction in blood pressure in this study. These outcomes challenge previous studies which found significant differences in systolic blood pressures after propofol administration in other patient populations.

Ebert et al. and Pandey et al. [14, 15] both found statistically significant declines in SBP following the administration of propofol in patients undergoing elective surgical procedures. There are several explanations which may contribute to the differing outcomes in our patient population. In our study, anesthesiologists customized the dosing of propofol and etomidate to take into account varied patient parameters including weight, age, injury, and hemodynamics. Our mean propofol dose was 127 mg which is lower than standard dosing of 2–2.5 mg/kg for an average weight 70 kg patient under the age of 55 which was utilized in previous studies [14, 15]. This reduced dosing of propofol likely reflected the anesthesiogist's efforts to account for possible hypovolemic states among patients. This strategy is consistent with previous findings which have suggested that modest reductions in propofol dose can still achieve desired effects in hypovolemic patients [26, 27]. Administration of propofol at a reduced dose may thus be a reasonable alternative to etomidate in patients with suspected hypovolemia.

An additional explanation for our differing outcomes may be explained by the patient population studied. To assist with analgesia, patients undergoing elective procedures are often medicated with fentanyl which is an independent risk factor for hypotension. Reich et al. [28] describe this impact and other risk factors for hypotension including age over 50, baseline hypotension, increasing

fentanyl doses, and ASA of III or IV, in addition to propofol administration. Our patient population did not meet the majority of these risk factors as our study demographics consisted of a population of predominantly young, normotensive, males and did not get fentanyl at time of induction. Finally, it should be noted that trauma patients have a unique physiologic response which differs from the traditionally studied patient undergoing elective surgical intervention. Trauma patients have significant alteration in the hypothalamic–pituitary–adrenal axis coupled with a catecholamine-driven stress response leading to differing hemodynamic responses from elective surgical candidates [29].

The results of our study suggest that propofol's hemodynamic impact on the trauma patient may not be as significant as traditionally suggested when appropriately adjusted dosing is utilized. In addition, there are no current consensus guidelines recommending a standard regimen for RSI in trauma patients. The EAST guidelines for emergency tracheal intubation following traumatic injury were most recently published in 2012 and recommended neuromuscular blockade with succinylcholine among trauma patients but provide no recommendation regarding specific induction agent [9]. In 2010, the Clinical Practice Committee of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine released guidelines for general anesthesia in emergency situations and noted that ketamine should be considered for hemodynamically compromised patients [30]. Ketamine may be an additional option for RSI and is increasingly being discussed as a viable induction agent in the emergent setting RSI [31], but our data set does not allow us to examine this question directly.

Limitations

Our study has several notable limitations. First, it is important to note that this study utilizes historical cohort data and does not reflect randomization or controls. However, the number who received propofol was larger, and the pre–post effect sizes in this group were very small, suggesting that low power was most likely not responsible for the propofol effects found here. In addition, in the era, when both propofol and etomidate were readily available, there may have been a selection bias among providers. Our study also did not address the amount of fluid resuscitation or blood transfusion, and therefore did not control for the effect or amount of resuscitation received by patients enrolled. Finally, our study includes a very limited population of hypotensive patients which suggests that the data collected here are applicable primarily to those patients presenting to the trauma bay with normal or high blood pressures only. This is a population where hemodynamic effects may be less consequential. Given that critically injured patients are often hypotensive, additional research is necessary to identify whether these trends in hemodynamics will be similar in hypotensive patients.

Conclusion

Our data show that etomidate and propofol do not have a statistically significant impact on the hemodynamics of normotensive and hypertensive trauma patients. When administered at reduced doses, propofol may represent a reasonable alternative to etomidate for RSI among normotensive and hypertensive trauma patients. However, further research is necessary to fully evaluate its safety in the acutely injured, hypovolemic patient.

Conflict of interest S. Zettervall, S. Sirajuddin, S. Akst, C. Valdez, C. Golshani, R. Amdur, B. Sarani, and J. Dunne declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was not needed in this study.

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