

# **Impact of Resuscitation Adjuncts on Post-Intubation Hypotension in Patients with Isolated TBI**

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## ABSTRACT

**Introduction:** Post-intubation hypotension (PIH) is a risk factor of endotracheal intubation (ETI) after injury. For those with traumatic brain injury (TBI), one episode of hypotension can potentiate that injury. This study aims to identify the resuscitation adjuncts which may decrease the incidence of PIH in this patient population.

**Methods:** This is a 4-year (2019-2022) prospective observational study at a level I trauma center. Adult ( $\geq 18$ ) patients with isolated TBI requiring ETI in the trauma bay were included. Blood pressures were measured 15 minutes pre- and post-intubation. Primary outcome was PIH, defined as a decrease in SBP  $\geq 20\%$  from baseline or to  $\leq 80$  mmHg, or any decrease in MAP to  $\leq 60$  mmHg. Multivariable logistic regression was performed to identify the associations of pre-intubation vasopressor, hypertonic saline (HTS), PRBC, and crystalloids on PIH incidence.

**Results:** Of the 490 enrolled patients, 16% had mild (Head AIS  $\leq 2$ ), 35% moderate (Head AIS 3-4), and 49% severe (Head AIS  $\geq 5$ ) TBI. Mean age was  $42 \pm 22$  years and 71% were male. Median ISS, head-AIS, and GCS were 26[19-38], 4[3-5], and 6[3-11], respectively. Mean SBP 15 minutes pre- and post-intubation were  $118 \pm 46$  and  $106 \pm 45$ , respectively. Before intubation, 31% received HTS, 10% vasopressors, 20% crystalloids, and 14% at least one unit of PRBC (median, 2[1-2]U). Overall, 304 (62%) patients developed PIH. On multivariable regression analysis, pre-intubation use of vasopressors and HTS were associated with significantly decreased odds of PIH independent of TBI severity, 0.310 (0.102-0.944,  $p = 0.039$ ) and 0.393 (0.219-0.70,  $p = 0.002$ ) respectively.

**Conclusions:** Nearly two-thirds of isolated TBI patients developed PIH. Pre-intubation vasopressors and HTS are associated with a decreased incidence of PIH. Such adjuncts should be considered prior to ETI in patients with suspected TBI.

**Level of Evidence:** III; Prospective Observational

**Keywords:** brain; hypotension; post-intubation; trauma

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## INTRODUCTION

There is an increased recognition of the importance of optimizing circulatory support prior to endotracheal intubation (ETI) in trauma patients (1). Post-intubation hypotension (PIH) is a not infrequent complication of ETI in the emergent setting, with incidence cited as high as 60% (2,3). Vasodilation caused by induction agents, coupled with the introduction of positive pressure ventilation, impedes preload and contributes to hypotension (4,5). Hypotension is a well-established risk factor for increased mortality in trauma patients, as well as those with isolated traumatic brain injury (TBI) (6,7).

PIH is well studied in critically ill non-trauma patients (8,9). However, there is a paucity of literature focused on PIH in the trauma bay and a dearth of data in isolated TBI patients (10). The rate of ETI in moderate-to-severe TBI patients is cited to be as high as 35% (11). Despite the frequency of intubation in TBI patients, the incidence, and potential preventative measures for PIH, in this important subset remains unknowns. In addition, this problem is further complicated by the lack of standardized (rapid sequence intubation) RSI techniques, and different RSI meds which may have a varying impact on individual patient hemodynamics.

Given the negative physiologic impact of hypotension this study aims to determine the prevalence, risk factors, and resuscitation adjuncts that may prevent or minimize PIH in isolated TBI patients.

## **METHODS**

### **Study design and population**

This is a prospective observational study of all adult trauma patients with isolated traumatic brain injury (TBI) presenting to our American College of Surgeons (ACS) verified Level I trauma center over 4 years (2019-2022). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were implemented for this study (please see **Supplemental Digital Content, <http://links.lww.com/TA/D639>**). This protocol was approved by our University Institutional Review Board. Written informed consent was waived due to the observational nature of the study.

### **Inclusion and exclusion criteria**

All adult ( $\geq 18$  years) trauma patients with isolated blunt TBI admitted to our trauma center requiring ETI in the trauma bay were included in the study. Isolated TBI was defined as isolated intracranial traumatic pathology diagnosed in the initial computed tomography (CT) scan and the absence of severe extracranial injuries (other body region abbreviated injury scale [AIS]  $<3$ ). The severity of TBI was categorized based on the head AIS into mild (Head AIS  $\leq 2$ ), moderate (Head AIS 3-4), and severe (Head AIS  $\geq 5$ ). Only patients with completion scans were included in the study. We excluded patients arriving in traumatic arrest and patients who were not intubated with medications for rapid sequence intubation (RSI).

### **Patient stratification**

Blood pressure (BP) was monitored in the trauma bay upon arrival. The closest recorded BP measurements within 15 minutes before and after intubation were documented. Patients were



stratified for analysis into two groups: those who developed post-intubation hypotension (PIH), and those who did not develop post-intubation hypotension (No-PIH).

PIH was defined according to the previous literature (10) as follows: (a) decrease in SBP to 80 mm Hg or less or a decrease in SBP of  $\geq 20\%$  from baseline; (b) decrease in mean arterial pressure (MAP) to  $\leq 60$  mm Hg; (c) among patients with pre-intubation hypotension (SBP  $\leq 90$  mm Hg before ETI) PIH was defined as an additional decrease in SBP more than 5 mm Hg; or (d) the administration or increase in the infusion rate of vasopressor medications. According to the institutional protocol, the emergency medicine team, composed of a resident and attending, is responsible for intubation of every trauma patient presenting to the trauma bay.

### **Data points**

Patients' vital signs in the trauma bay (systolic blood pressure [SBP], heart rate [HR], Shock Index [defined as HR divided by SBP], and Glasgow Coma Scale [GCS] score) were monitored by trained research personnel from arrival until 15 minutes after the intubation for all isolated TBI patients. The time of intubation from arrival, development of PIH, or post-intubation cardiac arrest in the trauma bay were recorded. We retrospectively recorded the following data points using electronic medical records for each subject: patient demographics (age, gender, race, and ethnicity), comorbidities (hypertension [HTN], diabetes mellitus [DM], pre-injury anticoagulants, substance abuse disorder, history of smoking), pre-intubation sedative agents (etomidate, ketamine, and propofol) and paralytic agents (succinylcholine, rocuronium) utilized for rapid sequence intubation (RSI), total (pre- and post- intubation) crystalloids

transfusion (normal saline [NS], 3% hypertonic saline [HTS]), and transfusion parameters (packed red blood cells [pRBCs], platelets, fresh frozen plasma [FFP]), PIH, and mortality.

### **Outcome measures**

The outcome measure of the study was the development of PIH among isolated TBI patients requiring ETI in the trauma bay.

### **Statistical analysis**

Descriptive statistics were employed. Continuous normally distributed variables were reported using means with standard deviation, and all non-normally distributed continuous variables were reported using medians with interquartile range. Categorical variables were summarized as proportions. The independent samples *t*-test and the Mann-Whitney U test were used to compare the means and medians to analyze differences between groups on a univariate level. Pearson's  $\chi^2$  tests were performed to compare categorical variables. To adjust for confounding factors and assess the independent association of resuscitation adjuncts with PIH, we performed multivariable regression analyses. Potential confounding variables were entered into the model based on existing literature, expert consensus, and variables with a  $p < 0.2$  on the univariable analysis. Variables input into the regression analyses included patient demographics (age and gender), time to intubation, emergency department vitals (shock index [SI] and GCS), injury characteristics, sedative and paralytic agents utilized, and crystalloids and blood product transfusions received.

Alpha ( $\alpha$ ) was set at 5%, and a  $p$ -value cutoff of  $<0.05$  was chosen for statistical significance. All the statistical analyses were performed on Statistical Package for Social Services (SPSS, version 29; SPSS, Inc., Armonk, NY).

## RESULTS

### Patient characteristics

Over a four-year period, 490 patients with isolated blunt TBI requiring ETI in the trauma bay were enrolled. Of these, 304 (62%) developed PIH. In this group of patients there were no intubations that were not successful. In addition, no patients were in arrest at the time of intubation. Notably, some patients met more than one criterion for inclusion in the PIH group. Among the study population, 16% had mild (Head AIS $\leq$ 2), 35% moderate (Head AIS 3-4), and 49% severe (Head AIS $\geq$ 5) TBI. **Figure 1** demonstrates the patient flow diagram of the study cohort.

The majority were White (88%) and male (70.6%) with a mean  $\pm$  SD age of  $42 \pm 22$  years, who required early intubation with a median [IQR] time to intubation of 41 [31-56] minutes. Overall, there was no statistically significant difference among study groups in terms of patients age, gender, race, and BMI ( $p<0.05$ ). However, patients with PIH were more likely to have a lower pre-intubation SBP (mean, mm Hg, 122 vs. 139,  $p<0.001$ ), higher shock index (mean, 0.9 vs 0.7,  $p<0.001$ ) and lower GCS (median, 4 vs. 8,  $p<0.001$ ) on presentation. The median [IQR] head AIS was 4 [3-5], with patients developing PIH having higher median head AIS (5 vs 4,  $p<0.001$ ). Of note, 23 (4.7%) patients were intoxicated and were intubated despite low ( $\leq$ 2) head AIS. Of those with PIH, 46 (15.1%) patients suffered post-intubation cardiac

arrest. Overall, 24-hour and in-hospital mortality were 13.3% and 35.1%, respectively. **Table 1** summarizes the baseline characteristics and mortality of the study cohort based on the presence and absence of PIH.

### **Transfusion requirements**

When exploring the pre-intubation transfusion requirements, 96 (19.4%) patients received pre-intubation normal saline, with no statistical difference in the mean volume infused between the study groups (PIH: 156 ml vs. No-PIH: 193 ml,  $p=0.398$ ). Overall, 71 (14.5%) received at least 1 unit of PRBC, 14 (2.9%) at least 1 unit of FFP, and 3 (0.6%) at least 1 unit of Platelets. Patients in the PIH group were more likely to receive pre-intubation vasopressor agents (12.1% vs. 6.5%,  $p=0.040$ ), with epinephrine being the most common agent used (10.5% vs. 5.4%,  $p=0.048$ ). Overall, 154 (31.4%) of our cohort had HTS transfusion prior to intubation (ranging from 100 to 1000 ml), with patients with PIH less likely to receive HTS (PIH: 27.0% vs. No-PIH: 38.7%,  $p=0.007$ ). **Table 2** summarizes the transfusion requirements of our study population based on the presence or absence of PIH.

### **Sedative and paralytic agents**

There was no statistically significant difference among study groups in the type and dose of sedative and paralytic agents administered for RSI ( $p>0.05$ ). The most common sedative and paralytic agents administered were etomidate (88%) and succinylcholine (83.3%), respectively. **Table 3** summarizes the pre-intubation sedative and paralytic agents used for RSI based on the presence and absence of PIH.

## **Independent associations of resuscitation adjuncts on PIH incidence**

On multivariable regression analysis, pre-intubation use of vasopressors (aOR, 0.310 [0.102-0.944];  $p = 0.039$ ) and HTS (aOR 0.393, 95%CI [0.219-0.706],  $p = 0.002$ ) were significantly associated with decreased odds of PIH development regardless of TBI severity, while administration of pre-intubation crystalloids (aOR 1.474, 95%CI [0.730-2.977],  $p = 0.279$ ) and pre-intubation PRBC transfusion (aOR 1.350, 95%CI [0.747-2.443],  $p = 0.320$ ) were not protective for PIH. **Table 4** demonstrates the independent effect of resuscitation adjuncts on PIH incidence. When excluding patients who had suffered prehospital cardiac arrest ( $n=80$ ), we identified 410 patients, of which 239 (58.3%) developed PIH. In this group, administration of HTS and pre-intubation vasopressors were significantly associated with a decreased odds of the incidence of PIH (**Table 5**).

## **Sub-analysis of PIH sub-categories**

Among the study population ( $n=490$ ), 304 (62%) developed PIH, of which 230 patients were included by criteria a and b (initial SBP $>90$ mmHg), and 74 patients by criteria c and d (Initial SBP $\leq 90$  mmHg). On the multivariable regression sub-analyses, 3% hypertonic saline and pre-intubation vasopressors were associated with decreased odds of PIH among both study sub-groups (patients with PIH included by criteria A and B vs. those with initial SBP $>90$ mmHg and patients with PIH included by criteria C and D vs. those with initial SBP $\leq 90$  mmHg). The results of sub-analyses are summarized in **Supplemental Table**, <http://links.lww.com/TA/D640>.

## **Discharge disposition**

Patients who had not sustained an episode of PIH in the trauma bay were significantly more likely to be discharged home and rehabilitation facilities compared to their No-PIH counterparts (29.6% vs 10.2%,  $p < 0.001$  and 24.2% vs 15.1%,  $p = 0.012$ , respectively) (**Table 6**). Discharge to a skilled nursing facility and long-term care facility were not significantly different between the two groups. Notably, a significantly greater number of patients had died in the PIH group compared to the No-PIH group (42.8% vs 22.6%,  $p < 0.001$ ).

## **DISCUSSION**

In our study, PIH occurred in nearly two-thirds of patients with isolated TBI requiring emergent ETI in the trauma bay. Administration of vasopressors and HTS prior to ETI were associated with decreased risk-adjusted odds of developing PIH. However, administration of crystalloids or PRBCs prior to intubation was not protective for PIH. Our data showed, not surprisingly, with increasing severity of TBI, the proportion of patients undergoing ETI also increases. In moderate to severe TBI patients, establishing a secure airway is a mainstay in initial management. However, the incidence of PIH in isolated TBI patients is not well known. In our study patients with moderate TBI and severe TBI had an incidence of PIH of 31.3% and 56.9%, respectively. Discharge disposition also appeared to be worse in patients that sustained an episode of PIH in the trauma bay. Patients that did not sustain PIH were more likely to go home or to a rehabilitation facility. The deleterious effects of hypotension, even for short periods, on the outcomes of TBI patients, are well established (12,13). Given the frequent need for ETI among TBI patients, and the increased risk of worsening the secondary injury, it is important to

understand the risk factors and preventive measures to avoid catastrophic events due to PIH in this subset of patients.

Existing data on PIH is primarily based on critical care literature. In these studies, there is a mixed population of trauma and non-trauma patients (14). The incidence of PIH in critically ill patients has been reported between 20% - 46% (1,10,15). However, there are limited studies specifically investigating the incidence of PIH solely in trauma patients and none, to our knowledge, in isolated TBI patients (10). In a retrospective study including 477 trauma patients, Green et al. reported a PIH prevalence rate of 36% (10). However, the objective of their study was to determine prevalence in the general trauma population.

There are no standard preventive measures known to avoid PIH. Moreover, the practices for emergency ETI vary between providers and centers. In a cross-sectional survey by the Canadian Critical Care Trials Group including 1,758 physicians, 54% reported using regular pre-intubation fluids or vasopressors prior to ETI (16). Importantly, 81% of the physicians reported that they always use intravenous fluids prior to ETI for trauma patients. On further questioning most responded that crystalloids were most commonly used. Only 4.9% of the physicians used vasopressors before ETI. In our study, vasopressor use was identified as a protective factor for preventing PIH, whereas transfusion of crystalloids, or, PRBC, was not independently associated with reduction in the odds of PIH. The manner of administration for certain pressors, such as epinephrine, were a combination of push and/or infusions. The exact amount These findings indicate the need for prioritization of particular resuscitation adjuncts upon initial presentation to the trauma bay in isolated TBI patients.

Hypertonic saline (HTS) is a regularly utilized adjunct in TBI patients to minimize cerebral edema and resulting secondary injury to the brain (17,18). It has additional benefits such as volume expansion, potentially modulating immune function, and reduction of multiple organ dysfunction (18–20). Wade et al, studied a cohort of trauma patients with TBI and hypotension and found that those who received hypertonic saline/dextran fluid (HTS/D) were twice as likely to survive as those who did not receive HTS/D (21). However, its association with the incidence of PIH has not been studied. Our data shows that the administration of HTS is protective and associated with decreased odds of developing PIH. Though more studies are needed to determine if this association is consistent in other studies, HTS, compared to other adjuncts, is a low-risk addition to resuscitation of TBI patients.

There are controversial results on the role of vasopressors during resuscitation. Certain studies have reported increased mortality with vasopressor use early during the resuscitation. In a prospective observational study by Davis et al., use of phenylephrine before intubation during air transport in trauma patients, was associated with reversal of hypotension in 83% of the patients (22). Concerns have been raised regarding the risk of rebound hypertension after vasopressor use for ETI. However, there is no definitive evidence that vasopressor use leads to rebound hypertension (23). Fuchita et al. performed a propensity matched secondary analysis of 2 multicenter trials on ETI in critically patients, and reported that routine use of pre-intubation vasopressors was not associated with a lower incidence of PIH (24). Further studies must evaluate the role of routine vasopressor use before ETI in trauma patients.



Uninjured, the brain retains autoregulation and maintains perfusion over a wide range of blood pressures (25). However, after TBI self-regulation may be impaired in a significant number of patients, with perfusion potentially dependent on an adequate systolic blood pressure (25–27). Thus, patients with TBI are susceptible to secondary brain injury and increased risk of death from hypotension (25,28). Green et al reported that patients developing PIH have a significant increase in mortality compared to intubated trauma patients that did not develop PIH (10). Smischney et al. reported that the need for vasopressors after ETI is a surrogate marker for increased mortality (9). This indicates that patients requiring ETI may not necessarily be hypotensive prior to ETI. In our study, patients who developed PIH had a significantly lower median systolic blood pressure (SBP) prior to ETI than those who did not develop PIH (122 mmHg vs 139 mmHg, respectively). Though a SBP is not considered “hypotension”, it may be a predictor of hypotension in isolated TBI patients in which preventative measures may need to be undertaken. In our current study, 43% of the TBI patients that developed PIH died during the admission compared to 23% in the No-PIH group.

Our study has several limitations. Since the decision to intubate early in the patient’s hospital course was at discretion of treating physician, there is a possibility of selection bias due to variations in clinical decision-making. For those that were intubated with a mild to moderate TBI, ETI may have occurred secondary to obtundation from alcohol and/or drug intoxication or severe agitation that may have prohibited a safe physical examination. Autopsy data was not available in this study, therefore true confirmation of patient injury was based on the availability of CT scan results and AIS scoring. In addition, our center does not routinely use the Marshall or Rotterdam score to grade CT Head scans and is a limitation of this study. Although we defined

PIH based on the previous literature, there is no agreement on the standard definition of PIH. In addition, despite high volume and detailed data entry from electronic medical records, as well as patients/family reports, there remains a potential bias from unmeasurable confounding variables that might affect the results. An additional limitation in this study pertains to the severe TBI subset that may have been herniating or manifesting a Cushing's response during the intubation process. The rate of PIH in this subset, as well as the comparative mortality, would be interesting data to match, but difficult to capture, given the late, transient, and unreliable nature of its clinical presentation.

## **CONCLUSION**

Nearly two-thirds of isolated TBI patients requiring emergency ETI developed PIH. Administration of vasopressors and HTS were associated with decreased risk-adjusted odds of developing PIH. Given the deleterious effects of transient hypotension on the outcomes of TBI patients, early recognition of PIH and preventive measures are of paramount importance. More studies are needed to gain a better understanding of the incidence in trauma patients at other centers.

## **SUPPLEMENTAL DIGITAL CONTENT**

**SDC 1.** Strobe Guidelines

**SDC 2.** Author COI forms

**SDC 3.** Multivariable Regression Sub-Analysis, Independent Effect of Resuscitation Adjuncts on Development of Post-intubation Hypotension Among Patients Included with Criteria A and B and Criteria C and D

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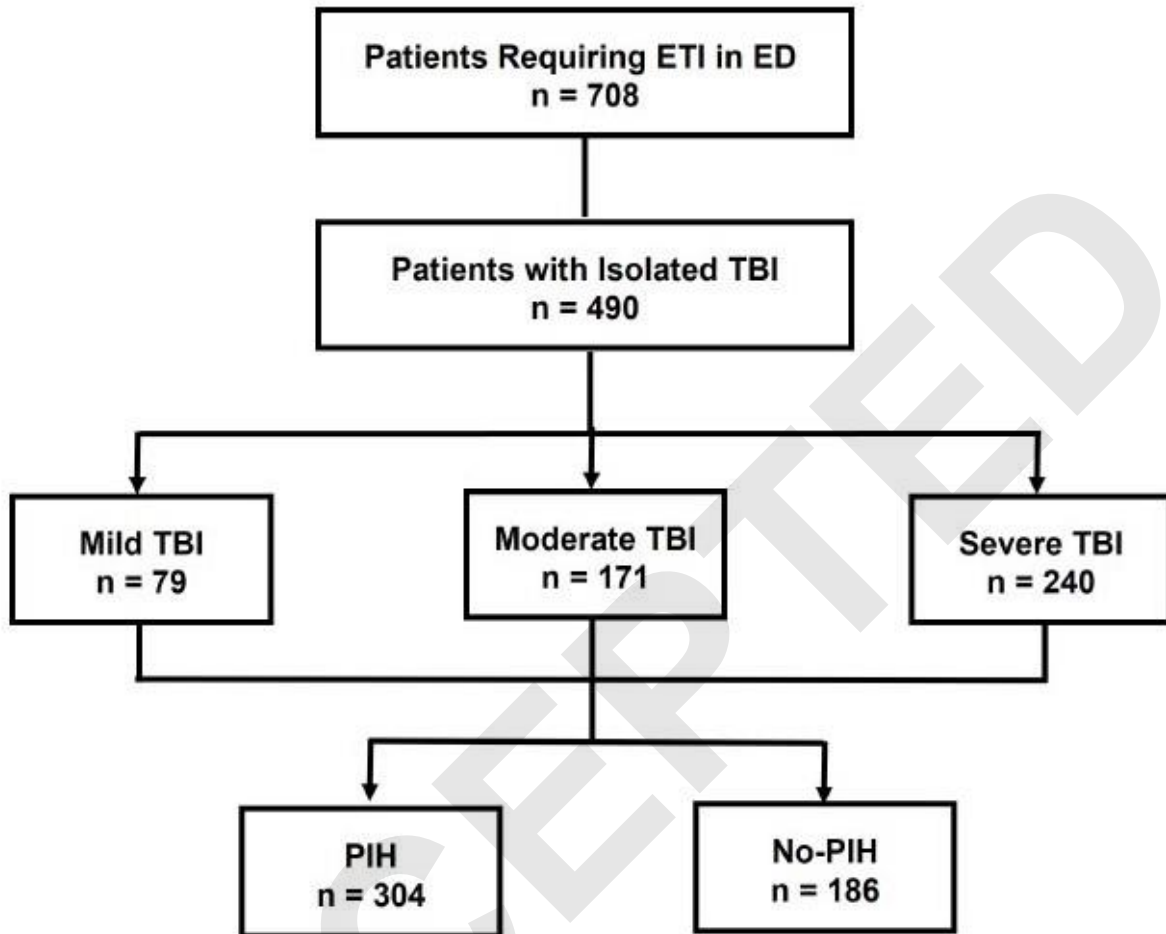


**FIGURE LEGEND**

**Figure 1.** The flow diagram of the study population

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Figure 1



**Table 1.** Baseline characteristics based on the presence or absence of Post-Intubation Hypotension (PIH)

Baseline Characteristics	Overall (N=490)	No-PIH (N=186)	PIH (N=304)	<i>p</i>
<b>Demographics</b>				
Age, years, mean ± SD	42 ± 22	42 ± 22	42 ± 21	0.932
Male Gender, n (%)	346 (70.6)	134 (72.0)	212 (69.7)	0.587
White, n (%)	431 (88.0)	164 (88.2)	267 (87.8)	0.910
BMI, kg/m <sup>2</sup> , median [IQR]	25 [22-30]	25 [22-29]	25 [21-30]	0.836
<b>ED Vitals</b>				
Pre-Intubation SBP, mmHg, mean ± SD	129 ± 40	139 ± 28	122 ± 45	<0.001
Pre-Intubation, HR, bpm, mean ± SD	99 ± 33	101 ± 26	97 ± 36	0.268
Pre-Intubation Shock Index, mean ± SD	0.8 ± 0.3	0.7 ± 0.2	0.9 ± 0.6	<0.001
O <sub>2</sub> Saturation, %, mean ± SD	93 ± 15	96 ± 4	91 ± 19	<0.001
GCS, median [IQR]	6 [3-11]	8 [6-12]	4 [3-9]	<0.001
<b>Time to Intubation, minutes, median [IQR]</b>	41 [31-56]	42 [31-60]	40 [30-55]	<0.001
<b>Injury Characteristics</b>				
Head AIS, median [IQR]	4 [3-5]	4 [3-5]	5 [3-5]	<0.001
Mild TBI, n (%)	79 (16.1)	43 (23.1)	36 (11.8)	<0.001
Moderate TBI, n (%)	171 (34.9)	76 (40.9)	95 (31.3)	0.030
Severe TBI, n (%)	240 (49.0)	67 (36.0)	173 (56.9)	<0.001
<b>Mechanism of Injury</b>				
Fall, n (%)	76 (15.5)	48 (25.8)	28 (9.2)	<0.001
MVC, n (%)	180 (36.7)	65 (34.9)	115 (37.8)	
Pedestrian, n (%)	85 (17.3)	21 (11.3)	64 (21.1)	
Other, n (%)	149 (30.4)	52 (28.0)	97 (31.9)	
<b>Prehospital Characteristics</b>				
Transport Time, median [IQR]	41 [31-56]	42 [31-60]	40 [30-55]	0.135
Prehospital Cardiac Arrest, n (%)	80 (16.3)	15 (8.1)	65 (21.4)	<0.001
<b>Comorbidities</b>				
HTN, n (%)	48 (9.8)	24 (12.9)	24 (7.9)	0.070
DM, n (%)	18 (3.7)	6 (3.2)	12 (3.9)	0.680
Pre-injury Anticoagulants, n (%)	16 (3.3)	9 (4.8)	7 (2.3)	0.125
Substance Abuse Disorder, n (%)	18 (3.7)	2 (1.1)	16 (5.3)	0.017
Smoking, n (%)	49 (10.0)	21 (11.3)	28 (9.2)	0.456
<b>Drug Screen Results</b>				
Negative, n (%)	309 (63.1)	108 (58.1)	201 (66.1)	0.073
Marijuana, n (%)	48 (9.8)	26 (14.0)	22 (7.2)	0.015
Stimulants, n (%)	103 (21.0)	40 (21.5)	63 (20.7)	0.837
Other Drugs, n (%)	30 (6.1)	12 (6.5)	18 (5.9)	0.812
<b>Post-Intubation Cardiac Arrest, n (%)</b>	48 (9.8)	2 (1.1)	46 (15.1)	<0.001
<b>Mortality, n (%)</b>				
24-hr Mortality, n (%)	65 (13.3)	15 (8.1)	50 (16.4)	0.008
In-hospital Mortality, n (%)	172 (35.1)	42 (22.6)	130 (42.8)	<0.001

n=numbers; SD=standard deviation; ED= emergency department; SBP=systolic blood pressure; HR=heart rate; Shock Index= HR/SBP; GCS=Glasgow coma score; ISS= Injury Severity Score; AIS=abbreviated injury scale; IQR=interquartile range; MVC= motor vehicle collision; HTN= hypertension; DM= diabetes mellites; Stimulants = cocaine/amphetamine/methamphetamine; BAC= Blood Alcohol Concentration; \*BAC >80 mg/dl were considered as beyond legal limit.

**Table 2.** Crystalloid, transfusion, and vasopressor requirements based on the presence or absence of Post-Intubation Hypotension (PIH)

Transfusion Requirements	Overall (N=490)	No-PIH (N=186)	PIH (N=304)	<i>p</i>
<b>Pre-Intubation Total Crystalloids Volume (ml)</b>				
Normal Saline, ml, mean ± SD	170 ± 472	193 ± 546	156 ± 422	0.398
HTS Transfusion, n (%)	154 (31.4)	72 (38.7)	82 (27.0)	<b>0.007</b>
HTS 3%, ml, mean ± SD	126 ± 208	150 ± 209	111 ± 206	<b>0.020</b>
<b>Pre-Intubation Blood Product Requirements</b>				
≥1U PRBC, n (%)	71 (14.5)	14 (7.5)	57 (18.8)	<b>&lt;0.001</b>
PRBC, ml, mean ± SD	167 ± 486	193 ± 546	156 ± 422	0.398
≥1U FFP, n (%)	14 (2.9)	4 (2.2)	10 (3.3)	0.463
≥1U Platelet, n (%)	3 (0.6)	1 (0.5)	2 (0.7)	0.868
<b>Pre-Intubation Vasopressor agents, n (%)</b>				
Overall, n (%)	49 (10)	12 (6.5)	37 (12.1)	<b>0.040</b>
Epinephrine, n (%)	42 (8.6)	10 (5.4)	32 (10.5)	<b>0.048</b>
Dose, mg, median [IQR]	2[1-2.75]	2[0.75-2.75]	2[1-3]	0.876
Norepinephrine, n (%)	4 (0.8)	0 (0.0)	4 (1.3)	0.116
Dose, mg, median [IQR]	16[8-16]	-	16[8-16]	-
Phenylephrine, n (%)	3 (0.6)	2 (1.1)	1 (0.3)	0.304
Dose, mg, median [IQR]	-	-	-	-

n=numbers; SD=standard deviation; HTS= hypertonic saline; ml= milliliter; PRBC= packed red blood cells; FFP= fresh frozen plasma

**Table 3.** Pre-intubation agents for rapid sequence intubation based on the presence or absence of Post-intubation Hypotension (PIH)

<b>Pre-Intubation Agents for RSI</b>	<b>Overall (N=490)</b>	<b>No-PIH (N=186)</b>	<b>PIH (N=304)</b>	<b><i>p</i></b>
<b>Sedative agents</b>				
Etomidate, n (%)	431 (88.0)	162 (87.1)	269 (88.5)	0.646
Etomidate, mg, median [IQR]	20 [20-20]	20 [20-20]	20 [20-20]	0.215
Ketamine, n (%)	46 (9.4)	17 (19.1)	29 (9.5)	0.883
Ketamine, mg, median [IQR]	45 [30-60]	45 [30-60]	45 [30-60]	0.667
Propofol, n (%)	13 (2.7)	7 (3.8)	6 (2.0)	0.232
Propofol, mg, median [IQR]	40 [25-95]	35 [21-57]	50 [25-100]	0.215
<b>Paralytic agents</b>				
Succinylcholine, n (%)	408 (83.3)	162 (87.1)	246 (80.9)	0.076
Succinylcholine, mg, median [IQR]	100 [100-120]	100 [100-120]	100 [100-120]	0.448
Rocuronium, n (%)	82 (16.7)	24 (12.9)	58 (19.1)	0.076
Rocuronium, mg, median [IQR]	100 [80-100]	100 [70-100]	100 [80-100]	0.110

n=numbers; mg= Milligram; IQR=interquartile range

**Table 4.** Multivariable regression analysis, independent effect of resuscitation adjuncts on development of Post-intubation Hypotension among patients with isolated TBI

<b>Variables</b>	<b>aOR</b>	<b>95% CI</b>	<b><i>p</i></b>
<b>Pre-Intubation Crystalloid</b>	1.474	0.730-2.977	0.279
<b>3% Hypertonic Saline</b>	0.393	0.219-0.706	<b>0.002</b>
<b>≥1 Unit of Pre-intubation PRBC</b>	1.350	0.747-2.443	0.320
<b>≥1 Unit of Pre-intubation FFP</b>	1.003	0.571-1.760	0.992
<b>Pre-Intubation Vasopressors</b>	0.310	0.102-0.944	<b>0.039</b>

PRBC=packed red blood cells; FFP= fresh frozen plasma; aOR=adjusted odds ratio; CI=confidence interval

**Table 5.** Multivariable regression analysis, independent effect of resuscitation adjuncts on development of Post-Intubation Hypotension among patients with isolated TBI, excluding patients with pre-hospital cardiac arrest

<b>Variables</b>	<b>aOR</b>	<b>95% CI</b>	<b><i>p</i></b>
<b>Pre-Intubation Crystalloid</b>	1.106	0.677-1.808	0.687
<b>3% Hypertonic Saline</b>	0.546	0.345-0.864	<b>0.010</b>
<b>≥1 Unit of Pre-intubation PRBC</b>	1.481	0.594-3.481	0.421
<b>≥1 Unit of Pre-intubation FFP</b>	1.939	0.507-7.419	0.333
<b>Pre-Intubation Vasopressors</b>	0.585	0.481-0.672	<b>0.002</b>

PRBC=packed red blood cells; FFP= fresh frozen plasma; aOR=adjusted odds ratio; CI=confidence interval

**Table 6.** Discharge disposition in patients with PIH versus no PIH

<b>Discharge Disposition</b>	<b>Overall (N=490)</b>	<b>No-PIH (N=186)</b>	<b>PIH (N=304)</b>	<b><i>p</i></b>
Discharge to Home, n (%)	86 (17.6)	55 (29.6)	31 (10.2)	<b>&lt;0.001</b>
Discharge to SNF, n (%)	27 (5.5)	7 (3.8)	20 (6.6)	0.185
Discharge to Rehab, n (%)	91 (18.6)	45 (24.2)	46 (15.1)	<b>0.012</b>
Discharge to LTCH, n (%)	24 (4.9)	11 (5.9)	13 (4.3)	0.415
Expired, n (%)	172 (35.1)	42 (22.6)	130 (42.8)	<b>&lt;0.001</b>

LTCH= long-term care hospital; SNF= Skilled Nursing Facility; Rehab=Rehabilitation Facility



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract ( <b>abstract methods</b> ) (b) Provide in the abstract an informative and balanced summary of what was done and what was found. ( <b>abstract results and conclusion</b> )
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ( <b>page 1</b> )
Objectives	3	State specific objectives, including any prespecified hypotheses ( <b>page 1</b> )
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper ( <b>page 1,2,3,4</b> )
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ( <b>page 2,3,4</b> )
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ( <b>page 2,3</b> ) (b) For matched studies, give matching criteria and number of exposed and unexposed ( <b>n/a</b> )
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ( <b>page 3,4</b> )
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ( <b>page 2,3</b> )
Bias	9	Describe any efforts to address potential sources of bias ( <b>page 4,10</b> )
Study size	10	Explain how the study size was arrived at ( <b>page 3,4; figure 1</b> )
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ( <b>page 3,4</b> )
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding ( <b>page 3,4</b> ) (b) Describe any methods used to examine subgroups and interactions ( <b>page 3,4</b> ) (c) Explain how missing data were addressed ( <b>n/a</b> ) (d) If applicable, explain how loss to follow-up was addressed ( <b>n/a</b> ) (e) Describe any sensitivity analyses ( <b>n/a</b> )
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ( <b>page 4,5</b> ) (b) Give reasons for non-participation at each stage ( <b>n/a</b> ) (c) Consider use of a flow diagram ( <b>figure 1; supplemental attachment</b> )
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ( <b>page 5,6,7; table 2-6, page 18,19,20,21,22</b> ) (b) Indicate number of participants with missing data for each variable of interest ( <b>n/a</b> ) (c) Summarise follow-up time (eg, average and total amount) ( <b>n/a</b> )
Outcome data	15*	Report numbers of outcome events or summary measures over time ( <b>page 5,6; table 1, page 17</b> )

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ( <b>page 4</b> ) (b) Report category boundaries when continuous variables were categorized ( <b>page 3,4</b> ) (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ( <b>n/a</b> )
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ( <b>page 6,7</b> )
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives ( <b>page 7</b> )
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ( <b>page 10</b> )
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ( <b>page 7-11</b> )
Generalisability	21	Discuss the generalisability (external validity) of the study results ( <b>page 7</b> )
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ( <b>page 12</b> )

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

**e Table – Multivariable Regression Sub-Analysis, Independent Effect of Resuscitation Adjuncts on Development of Post-intubation Hypotension Among Patients Included with Criteria A and B and Criteria C and D**

<b>Patients with Initial SBP&gt;90 mmHg: PIH Included by Criteria A and B vs. no PIH</b>			
<b>Variables</b>	<b>aOR</b>	<b>95% CI</b>	<b>p</b>
Pre-Intubation Crystalloid	0.979	0.585-1.637	0.934
3% Hypertonic Saline	0.611	0.400-0.932	<b>0.022</b>
≥1 Unit of Pre-intubation PRBC	1.910	0.671-4.439	0.642
≥1 Unit of Pre-intubation FFP	0.416	0.099-1.748	0.231
Pre-Intubation Vasopressors	0.385	0.139-0.815	<b>0.008</b>
<b>Patients with Initial SBP≤90 mmHg: PIH Included by Criteria C and D vs. no PIH</b>			
<b>Variables</b>	<b>aOR</b>	<b>95% CI</b>	<b>p</b>
Pre-Intubation Crystalloid	0.466	0.013-6.829	0.677
3% Hypertonic Saline	0.759	0.280-0.880	<b>0.006</b>
≥1 Unit of Pre-intubation PRBC	0.924	0.684-1.084	0.068
≥1 Unit of Pre-intubation FFP	0.999	0.841-1.842	0.866
Pre-Intubation Vasopressors	0.466	0.133-0.871	<b>0.007</b>

PRBC=packed red blood cells; FFP= fresh frozen plasma; aOR=adjusted odds ratio; CI=confidence interval

## CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

**Date:** 11/30/2023

**Your Name:** Megan Lundy

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.]

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related or unrelated to the content of your manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

Participants of an accredited activity must disclose all personal **financial** and **non-financial relationships**, over the previous 36 months with an **ineligible company** (formerly defined as a commercial interest). **Financial relationships** are those relationships in which the individual benefits by receiving a salary, royalty, consulting fee, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest), or other financial benefits, and may affect activity content relevant to products or services of an **ineligible company**, defined as an entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

If the article is accepted, all author JTACS COI forms will be published as supplemental material with the article.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<b>Time frame: Since the initial planning of the work</b>			
1	All support for the present manuscript (e.g., funding, provision	<input checked="" type="checkbox"/> None	

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	of study materials, medical writing, article processing charges, etc.) <b>No time limit for this item.</b>		Click the tab key to add additional rows.
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8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
11	Stock or stock options	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

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**Date:** 11/30/2023

**Your Name:** Omar Hejazi

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.]

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related or unrelated to the content of your manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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	of study materials, medical writing, article processing charges, etc.) <b>No time limit for this item.</b>		Click the tab key to add additional rows.
<b>Time frame: past 36 months</b>			
<b>2</b>	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> <b>None</b>	
<b>3</b>	Royalties or licenses	<input checked="" type="checkbox"/> <b>None</b>	
<b>4</b>	Consulting fees	<input checked="" type="checkbox"/> <b>None</b>	
<b>5</b>	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> <b>None</b>	
<b>6</b>	Payment for expert testimony	<input checked="" type="checkbox"/> <b>None</b>	
<b>7</b>	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> <b>None</b>	



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8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
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13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	<input checked="" type="checkbox"/> None  <table border="1"><tr><td></td><td></td></tr><tr><td></td><td></td></tr><tr><td></td><td></td></tr></table>							

Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

## CONFLICT OF DISCLOSURE FORM

Based on ICMJE Form

**Date:** 12/1/2023

**Your Name:** Bellal Joseph, MD, FACS

**Manuscript Title:** Click or tap here to enter text.

**Manuscript Number (if known):** \_\_\_\_\_

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<b>1</b>	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article)	<input checked="" type="checkbox"/> <b>None</b>   	   Click the tab key to add additional rows.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	processing charges, etc.) <b>No time limit for this item.</b>		
<b>Time frame: past 36 months</b>			
<b>2</b>	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> <b>None</b>	
		DOD grant	Money to institution
		NIH grant	Money to institution
<b>3</b>	Royalties or licenses	<input checked="" type="checkbox"/> <b>None</b>	
<b>4</b>	Consulting fees	<input checked="" type="checkbox"/> <b>None</b>	
<b>5</b>	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> <b>None</b>	
		CSL Behring	Lecture - \$3000 in 2021
<b>6</b>	Payment for expert testimony	<input checked="" type="checkbox"/> <b>None</b>	
<b>7</b>	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> <b>None</b>	
		CSL Behring	Travel for educational event – \$610.38 in 2022

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)										
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> <b>None</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> </table>											
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10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input type="checkbox"/> <b>None</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>Editorial Board – Current Trauma Reports, Annals of Surgery Open Access, World Journal of Surgery, Journal of Trauma and Acute Care Surgery</td> <td>Unpaid</td> </tr> <tr> <td>Scientific Advisory Committee - CNTR</td> <td>Unpaid</td> </tr> <tr> <td>Director – EAST Manuscript &amp; Literature Review Committee</td> <td>Unpaid</td> </tr> </table>	Editorial Board – Current Trauma Reports, Annals of Surgery Open Access, World Journal of Surgery, Journal of Trauma and Acute Care Surgery	Unpaid	Scientific Advisory Committee - CNTR	Unpaid	Director – EAST Manuscript & Literature Review Committee	Unpaid					
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	spouse, partner, or children		
<p><b>Please place an "X" next to the following statement to indicate your agreement:</b></p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

ACCEPTED

## CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

**Date:** 11/30/2023

**Your Name:** Madolyn Conant

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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## CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

**Date:** 11/30/2023

**Your Name:** Lou Magnotti

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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<b>7</b>	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> <b>None</b>	

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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	
14	Family Disclosure. Disclose any financial associations involving a spouse, partner, or children	<input checked="" type="checkbox"/> None	

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## CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

**Date:** 11/30/2023

**Your Name:** Dylan Joule

**Manuscript Title:** [Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries]

**Manuscript Number (if known):** [Click or tap here to enter text.]

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<b>7</b>	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> <b>None</b>	

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## CONFLICT OF INTEREST DISCLOSURE FORM

Based on ICMJE Form

**Date:** 11/30/2023

**Your Name:** Christina Colosimo

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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**CONFLICT OF INTEREST DISCLOSURE FORM**

*Based on ICMJE Form*

**Date:** 11/30/2023

**Your Name:** Audrey Spencer

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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**CONFLICT OF INTEREST DISCLOSURE FORM**

*Based on ICMJE Form*

**Date:** 11/30/2023

**Your Name:** Adam Nelson

**Manuscript Title:** Avoiding a Second Hit: Resuscitation Adjuncts to Prevent Post-Intubation Hypotension in Patients with Isolated Traumatic Brain Injuries

**Manuscript Number (if known):** [Click or tap here to enter text.]

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## CONFLICT OF DISCLOSURE FORM

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**Date:** 6/30/2023

**Your Name:** Tanya Anand

**Manuscript Title:** Coming of Age: Modern Management of Gallbladder and Biliary disease in the Older Adult

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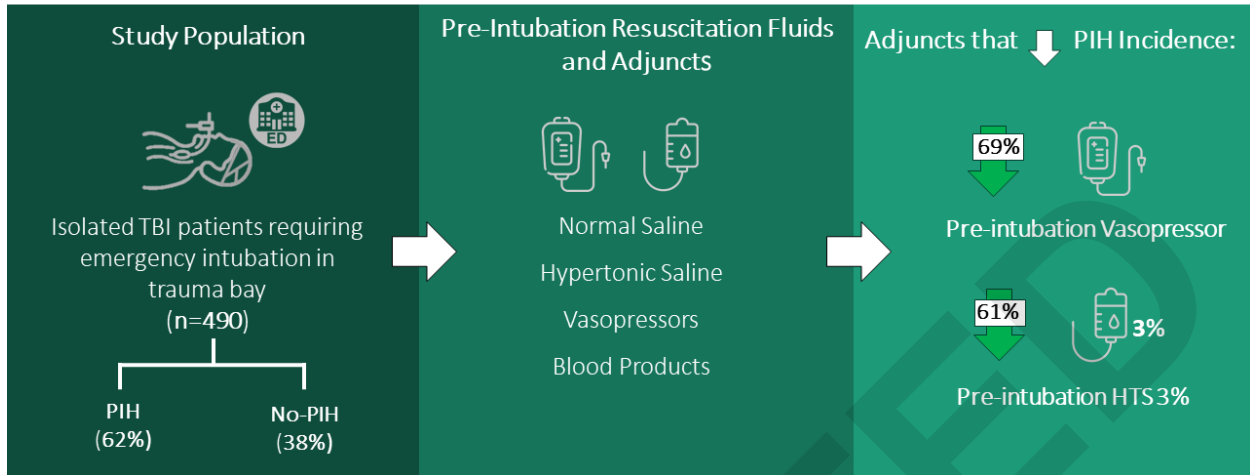
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## Impact of Resuscitation Adjuncts on Post-intubation Hypotension in Patients with Isolated TBI



Anand T et al. *Journal of Trauma and Acute Care Surgery*.  
DOI: 10.1097/TA.0000000000004306

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