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Association of Vasopressor Choice with Clinical and Functional Outcomes following Moderate-Severe Traumatic Brain Injury: A TRACK-TBI Study

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Thank you for considering this manuscript for publication in Neurocritical Care. We confirm that this manuscript complies with all instructions to authors. We confirm that authorship requirements have been met and the final manuscript was approved by all authors. We confirm that this journal has not been published elsewhere and is not under review or consideration by another journal. Data reported in this study were collected by trained research coordinators, using structured data collection tools. The present study was approved by the Institutional Review Board at Duke University. We have completed the STROBE checklist for observational studies to ensure the robustness of our study design and methods.

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Abstract

Background—Early hypotension following moderate-severe traumatic brain injury (TBI) is associated with increased mortality and poor long-term outcomes. Current guidelines suggest the use of intravenous vasopressors to support blood pressure following TBI; however, guidelines do not specify vasopressor type, resulting in variation in clinical practice. Minimal data are available to guide clinicians on optimal early vasopressor choice to support blood pressure following TBI. Therefore, we conducted a multicenter study to examine initial vasopressor choice for the support of blood pressure following TBI and its association with clinical and functional outcomes after injury.

Methods—We conducted a retrospective cohort study of patients enrolled in the TRACK-TBI study, an 18-center prospective cohort study of TBI patients evaluated in participating Level 1 trauma centers. We examined adults with moderate-severe TBI (defined as Glasgow Coma Scale score <13) who were admitted to the ICU and received an intravenous vasopressor within 48 hours of admission. The primary exposure was initial vasopressor choice (phenylephrine versus norepinephrine) and the primary outcome was 6-month Glasgow Outcomes Scale Extended (GOSE), with the following secondary outcomes: length of hospital stay, length of ICU stay, in-hospital mortality, new requirement for dialysis, and 6-month Disability Rating Scale (DRS). Regression analysis was used to assess differences in outcomes between patients exposed to norepinephrine versus phenylephrine, with propensity-weighting to address selection bias due to both the non-random allocation of the treatment groups and subject drop-out.

Results—The final study sample included 156 patients, of whom 79 (51%) received norepinephrine, 69 (44%) received phenylephrine, and 8 (5%) received an alternate drug as their initial vasopressor. 121 (77%) of patients were male, with a mean age of 43.1 years. Of patients receiving norepinephrine as their initial vasopressor, 32% had a favorable outcome (GOSE 5-8), while 40% of patients receiving phenylephrine as their initial vasopressor had a favorable outcome. Compared to phenylephrine, exposure to norepinephrine was not significantly associated with improved 6-month GOSE (weighted odds ratio 1.40, 95% CI 0.66-2.96, p=0.37) or any secondary outcome.

Conclusion—The majority of patients with moderate-severe TBI received either phenylephrine or norepinephrine as first-line agents for blood pressure support following brain injury. Initial choice of norepinephrine, compared to phenylephrine, was not associated with improved clinical or functional outcomes.

Keywords

traumatic brain injury; shock; vasopressors

Introduction

Traumatic brain injury (TBI) continues to be a significant public health burden in the United States, contributing to nearly 30% of all injury related deaths[1]. Moreover, moderate-severe TBI is a significant source of long-term disability, including significant declines in cognitive and motor function over the year following injury[1,2]. To help improve outcomes following TBI, guidelines for management of severe TBI are aimed at reducing primary and secondary

brain injury, including minimizing cerebral ischemia, intracranial hypertension, hypotension, and multi-organ failure[3,4]. In particular, early hypotension following moderate-severe TBI can cause cerebral ischemia, compromise cerebral hemodynamics, and is strongly associated with increased mortality and poor clinical outcomes following injury[5-9].

Given that optimal hemodynamics may be patient-specific, maintenance of systolic blood pressure (SBP) ≥100 mm Hg for patients 50 to 69 years and ≥110 mm Hg for patients 15 to 49 or ≥70 years old is supported by current guidelines[3,10,11]. However, no specific strategies to augment blood pressure (e.g., recommending a specific vasopressor agent) currently exist, resulting in observed variation in clinical practice based on prior literature[3,12-15]. Intravenous vasopressors, commonly phenylephrine or norepinephrine, are used to augment blood pressure and thereby increase cerebral perfusion pressure (CPP) following TBI, although their impact on cerebral vasculature remains unclear[16,17]. While vasopressors have been studied extensively in some critical care paradigms, such as septic shock, minimal data are available to guide clinicians on optimal early vasopressor choice to support blood pressure following TBI[16,18-21]. To address this gap, the aims of our study were to: 1) Describe vasopressor utilization patterns for the management of early hypotension following moderate-severe TBI and 2) Examine the association between initial vasopressor choice with clinical and functional outcomes following injury. We hypothesized that variation in initial vasopressor choice use would exist, and that norepinephrine would be associated with improved clinical outcomes.

Methods

Database and Study Design

We conducted a secondary analysis (retrospective cohort study) of adult patients enrolled in the Transforming Clinical Research and Knowledge in TBI (TRACK-TBI) prospective cohort study. TRACK-TBI is an 18-center cohort study of patients evaluated in a level 1 trauma center emergency department within 24 hours of suffering blunt TBI, for whom a clinically indicated head CT scan was obtained. Informed consent was obtained from patients or surrogate next of kin. In addition to collection of a multi-dimensional outcome battery over the year following injury, detailed hospital encounter data (including time-stamped diagnostic, pharmacy, and laboratory information) were also collected[22]. Subjects were excluded from the TRACK-TBI cohort if they met the following criteria: significant history of pre-existing conditions that would interfere with follow-up and outcome assessment; prisoners or patients in custody; pregnant; on psychiatric hold; major debilitating baseline mental health disorders or major debilitating neurologic disease; participants in an interventional trial; or penetrating head or spinal cord injury with ASIA score of C or worse[23]. Data were collected by trained research coordinators, using structured data collection tools. The present study was approved by the Institutional Review Board at Duke University.

Study Population

We examined adults (age>17 years) in the TRACK-TBI cohort with moderate-severe TBI, defined as Glasgow Coma Scale (GCS) score of <13 after resuscitation, who were

admitted to the Intensive Care Unit (ICU) and received vasopressors within 48 hours of hospital admission. Early vasopressor therapy after injury (within 48 hours) was chosen to increase the likelihood of injury-induced hypotension, rather than from subsequent hospital complications (such as septic shock or pulmonary embolism), and during a period when the brain is most sensitive to secondary injury. To avoid examining early mixed vasopressor therapies, we excluded patients who received more than one vasopressor within the first hour of initial vasopressor administration.

Exposure, Outcomes, and Covariates

The primary exposure was initial vasopressor choice within 48 hours of hospital admission following injury. Initial vasopressor choice was categorized as: phenylephrine, norepinephrine, and other vasopressor (vasopressin, dopamine, dobutamine, epinephrine, and ephedrine). Given that the vast majority of patients in the study cohort received phenylephrine or norepinephrine as the initial vasopressor, we considered these vasopressors as our primary exposures. Supported by the literature and subject matter expertise of the study team, these two vasopressors were deemed to likely represent the most commonly used vasopressors for management of hypotension following TBI in current clinical practice[15,18]. The primary outcome of interest was 6-month Glasgow Outcomes Scale Extended (GOSE), with GOSE 5-8 considered as a good outcome and GOSE 1-4 considered as a poor outcome[24,25]. Secondary outcomes examined included: length of hospital stay, length of ICU stay, in-hospital mortality, new requirement of dialysis, and 6-month Disability Rating Scale (DRS)[26].

Covariates examined include demographics characteristics (age, gender, race, ethnicity, education level), co-treatments (intracranial pressure monitoring, blood transfusion, receipt of osmotherapy, mechanical ventilation), and injury characteristics (injury cause, injury mechanism, Rotterdam score, presence of blood products on initial head computed tomography scan, Glasgow Coma Scale, Head Abbreviated Injury Score, non-head Injury Severity Score, ED mean systolic blood pressure).

Statistical Analysis

Descriptive statistics were used to examine demographic, clinical, and injury characteristics among the entire cohort, as well as stratified by the initial vasopressor used (phenylephrine, norepinephrine, and other). Kruskal-Wallis tests were used to evaluate these differences among continuous variables, and Fisher’s exact tests were used for categorical variables. Descriptive statistics were used to examine type and timing of second vasopressor agents, among patients who received a second vasopressor greater than one hour following initial vasopressor choice.

To examine associations of initial vasopressor choice with clinical outcomes, we restricted the population to patients receiving phenylephrine and norepinephrine as the initial vasopressor choice for hemodynamic management. We used inverse propensity-weighting to help account for bias due to the non-random allocation of treatment groups (confounding by indication) and subject drop-out (selection bias). Separate propensity models were constructed for both treatment (phenylephrine versus norepinephrine), missingness on

GOSE, and missingness on DRS using a boosted logistic regression algorithm based on the following covariates (selected based on prior literature, the authorship team's subject matter expertise, and use of a directed acyclic graph): age, gender, enrolling site, race, ethnicity, education level (as a surrogate for socioeconomic status), injury mechanism, emergency department (ED) GCS, CT result, head abbreviated injury score, non-head injury severity score, ED mean and systolic blood pressure, need for blood transfusion, need for osmotherapy (mannitol or hypertonic saline), placement of an intracranial pressure monitor, and need for mechanical ventilation. Scores from the group model were characterized as the propensity for being selected for the observed group the subject was in, then inverted so the higher weights were given to subjects who more closely matched the characteristics of the other group. Scores from the outcome models were characterized as the propensity of being followed, thus followed subjects who more closely resembled subjects with missing outcome received higher weights. Next, the group weight was multiplied by the respective outcome weight, and the resulting product was standardized so that the average weight for each subject always remained equal to one. Treatment effects for the primary and secondary outcomes were calculated using logistic regression (for binary outcomes), linear regression (for continuous outcomes), and Cox proportional hazards models for length of stay, with death considered as a censored event. In a sensitivity analysis, we examined the primary outcome of GOSE using ordinal logistic regression, to confirm the robustness of our outcome assessment. Given that we examined the total effect of initial vasopressor on clinical outcomes, we did not consider mediator variables (such as the need for additional vasopressors and hemodynamic responses to therapy) in our models, as these variables were considered to occur on the causal pathway between vasopressor choice and clinical outcomes. Given that we pre-specified a primary outcome for analysis, no additional statistical adjustments were made to account for multiple testing of the secondary outcomes. A p-value < 0.05 was considered statistically significant, and all analyses were performed using SPSS version 26 (Armonk, NY, USA).

Results

Demographic and Clinical Characteristics of Study Population

The final study population included 156 subjects from 17 different clinical sites in the TRACK-TBI cohort (Figure 1). Details on the demographic and clinical characteristics of the study population may be found in Table 1. Of the 156 subjects in our sample, 121 (78%) were male and had a mean age of 43.1 years (SD 17.3). White patients made up 81% (122) of the study population with 27 (18%) identifying as Hispanic. The mean (SD) GCS upon arrival was 5.0 (2.8), with a mean Injury Severity Score of 8.3 (9.2) and AIS head of 4.1 (1.1). The mean (SD) initial emergency department SBP was 140 mmHg (34) and MAP was 106 mmHg (26). Patients receiving norepinephrine and phenylephrine as initial vasopressors had similar baseline clinical characteristics, although utilization of norepinephrine versus phenylephrine as initial vasopressor choice varied by clinical study site.

Vasopressor Utilization

Through the study period, 79 (51%) patients received norepinephrine and 69 (44%) patients received phenylephrine as an initial vasopressor for the treatment of hypotension.

Only 8 (5%) individuals received an initial vasopressor other than norepinephrine and phenylephrine. Among all patients receiving vasopressors for hemodynamic management, 71 (46%) received a second vasopressor after at least one hour following administration of the first vasopressor, at a mean (SD) time from initial vasopressor administration to start of a second vasopressor of 27.8 hours (SD 39.6). 42 patients (59%) who received phenylephrine as an initial vasopressor received a second vasopressor, and 25 patients (35%) of patients who received norepinephrine as an initial vasopressor received a second vasopressor. Further details regarding choice of vasopressors, variation in the utilization, and overlap of initial and secondary vasopressor therapies are shown in Figure 2.

Clinical and Functional Outcomes

Supplemental Table 1 shows the covariate distribution pre- and post-propensity weighting. Table 2 shows primary and secondary clinical outcomes, among patients exposed to early norepinephrine versus phenylephrine. Of the 120 patients that had 6-month GOSE data available, we categorized each patient as having a favorable outcome (GOSE 5-8) or a poor outcome (GOSE 1-4). 32% of patients receiving norepinephrine as their initial vasopressor had a favorable outcome (GOSE 5-8), while 40% of patients receiving phenylephrine as their initial vasopressor had a favorable outcome (GOSE 5-8). Compared to phenylephrine, exposure to norepinephrine as initial vasopressor choice was not associated with improved 6-month GOSE (weighted odds ratio 1.40, 95% CI 0.66-2.96, p=0.38). Further, no significant associations were found with any secondary outcome, including 6-month DRS (p=0.78), length of hospital stay (p=0.53), length of ICU stay (p=0.31), in-hospital mortality (p=0.23), and need for dialysis (p=0.79). Sensitivity analysis using ordinal logistic regression demonstrated a stable risk estimate for the primary outcome of 6-month GOSE (weighted odds ratio 1.40, 95% CI 0.66-2.96, p=0.38). Figure 3 shows the distribution of GOSE among patients exposed to norepinephrine, compared to phenylephrine.

Discussion

We conducted a multicenter study to examine utilization patterns of different vasopressors for early hemodynamic management following TBI and their association with long-term clinical and functional outcomes. We found the following: 1) The most common vasopressors utilized for early hemodynamic management following moderate-severe TBI were norepinephrine and phenylephrine; and 2) There were no significant differences between those initially treated with norepinephrine, compared to those initially treated with phenylephrine, with regard to any of the clinical or functional outcomes examined.

Our findings regarding vasopressor utilization are consistent with prior research examining patterns of vasopressor utilization following TBI. A 2011 single-institution retrospective study of initial vasopressor use following severe TBI found a preference for phenylephrine as a first choice[18], while Dhillon et al.[15] found that norepinephrine was most common in a retrospective cohort study of 83 severe TBI patients. Despite variability in the choice of vasopressor, benefits of one vasopressor over another remain unclear based on current literature. Currently in clinical practice, the use of vasopressor therapy is for restoring and maintaining adequate cerebral perfusion pressure [CPP= mean arterial pressure (MAP)

– intracranial pressure (ICP)] by increasing MAP and thus ensuring cerebral blood flow (CBF) in accordance with metabolic demands[3]. Yet, vasopressor choice has been reported to have varying impacts on these measures of cerebral hemodynamics[16]. As a selective alpha-1 agonist, phenylephrine is often used as an arterial vasoconstrictor to increase MAP. Increase in MAP upon administration of phenylephrine incites subsequent reflex bradycardia, reduced cardiac output (CO), and has been associated with increased CBF, but paradoxically decreased cerebral tissue oxygen saturation[16,27,28]. Norepinephrine has predominantly alpha-1 agonist properties and mild-moderate beta-1 agonist properties, causing arterial vasoconstriction in addition to inotropic and chronotropic effects[27]. In healthy subjects, norepinephrine has been shown to increase MAP, sustain CO, but also decrease cerebral tissue oxygen saturation[29]. In pediatric patients, Di Gennaro et al.[19] found that norepinephrine, compared to phenylephrine, was associated with clinically relevant higher CPP 3 hours after start of vasopressor therapy. In adults, Sookplung et al.[18] found that TBI patients who received phenylephrine had significantly higher MAP and CPP for the 3 hours following initiation of vasopressor, compared to norepinephrine or dopamine. These mixed findings are reflected in a recent systematic review comparing vasopressor use with clinical outcomes, which found no evidence to favor norepinephrine over phenylephrine in augmenting CPP[20].

As we attempt to advance the practice of patients with TBI, it is also worth considering the underlying mechanisms of cerebral hemodynamic dysfunction that these vasoactive agents are intended to target. Normally, the cerebral circulation is maintained in homeostasis coupled to neuronal activity through a cerebral autoregulatory system involving cardiovascular, respiratory, and neural mechanisms[30-32]. Following severe brain injury, if autoregulation remains intact, a drop in blood pressure triggers autoregulatory vasodilation in an attempt to maintain adequate brain perfusion. This results in increased CBF which in turn elevates ICP. If autoregulation is not intact, there is dependency on SBP to prevent cerebral ischemia which has been ascribed to be the single most important secondary insult[8,9,33]. Nonetheless, there is evidence to suggest that norepinephrine and phenylephrine may have differential effects on cerebral hemodynamics[16,27-29].

Our study is the first to examine vasopressor choice and long-term clinical and functional outcomes following TBI. Based on the findings in this study, clinicians caring for TBI patients may consider not basing vasopressor choice on a “one size fits all” strategy, and consider opting for the use of other clinical variables to guide their selection of vasopressor to augment blood pressure and limit hypoperfusion[34]. For example, patients with TBI experiencing cardiogenic shock, septic shock, or evidence of systolic dysfunction on echocardiogram may benefit from a choice of norepinephrine over phenylephrine[34-36]. These observations are inferred from prior literature, but such conclusions would require testing in future studies. For patients without central venous access or those not benefiting from ionotropic and chronotropic effects of norepinephrine, clinicians may consider administration of phenylephrine[27,34]. Future studies comparing the effects of vasopressor therapy following TBI should consider the use of personalized measures of hemodynamic status (such as myocardial workload, autonomic function, and left ventricular ejection fraction from bedside echocardiography) and cerebrovascular reactivity to guide vasopressor

choice and conduct randomized controlled trials to help identify optimal vasopressor therapy[17,37-41].

There are several limitations to this study. First, data available from the TRACK-TBI study represented utilization across clinical sites at large Level 1 trauma centers and may not be representative of all clinical sites in the United States. Second, though the phenylephrine and norepinephrine groups demonstrated similar baseline demographic and clinical characteristics through propensity-weighting, significant variability was present between centers in initial choice of vasopressor. Third, despite the large sample size of TRACK-TBI overall, a relatively small number of cases met study entry criteria, potentially leading to decreased precision in the risk estimates from a lack of statistical power. Fourth, while detailed information on pharmaceutical exposures was available, information on underlying mechanisms for hypotension was not; thus, type of shock state (hemorrhagic, cardiogenic, obstructive, distributive) could not be assessed and may contribute to bias in the analysis. That being said, patients are often started on initial vasopressor without knowledge of the exact shock state (with the choice of vasopressor based on hospital culture), which is supported by our analysis given wide heterogeneity in initial vasopressor choice by study site. Fifth, lack of randomization into vasopressor groups introduces potential confounding by indication, specifically with regard to head injury severity; our study addressed this by employing causal inference framework and using propensity-weighted analytic methods, but may still be at risk for bias. Sixth, nearly half of the study population (46%) received a second vasopressor at a mean time of 27.8 hours following the first vasopressor; while we considered additional vasopressor use, fluid therapy, and blood pressure response as mediators on the causal pathway between initial vasopressor choice and clinical/functional outcomes (and did not adjust for these variables), this can make the effect of the initial vasopressor choice challenging to isolate. Lastly, despite the extensive clinical variables collected in the TRACK-TBI study, our observational study remains at risk for residual confounding.

Conclusion

In conclusion, in a multi-center population of moderate-severe TBI patients, significant variability of initial vasopressor choice was observed. Initial choice of norepinephrine, compared to phenylephrine, was not associated with improved clinical or functional outcomes. Further studies are required to better personalize vasopressor therapies for patients with brain injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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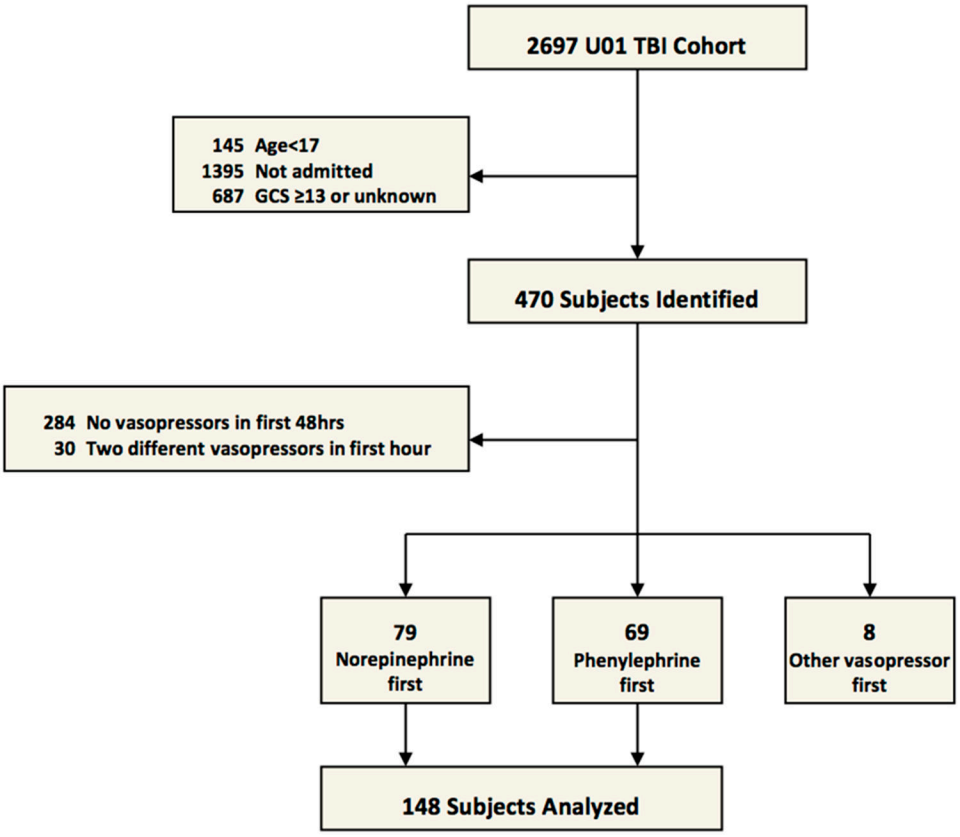
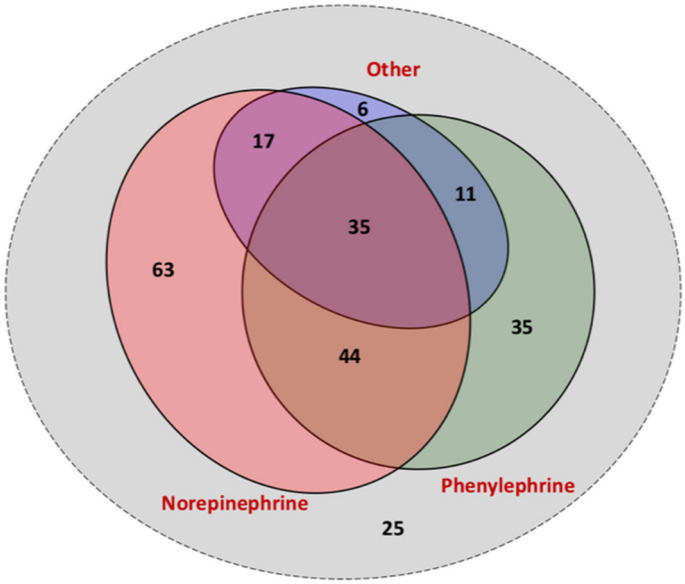


Figure 1:
STROBE diagram of inclusion and exclusion criteria



Vasopressor Use	N (%)
No Vasopressors*	259 (55%)
Norepinephrine only	63 (13%)
Phenylephrine only	35 (7%)
Other only	6 (1%)
Norepineph. & Phenyleph.	44 (9%)
Norepinephrine & Other	17 (4%)
Phenylephrine & Other	11 (2%)
All three types	35 (7%)
Total Subjects	**470**

*Of the 284 who received no vasopressors in the first 48 hours, 25 did eventually receive them.

Figure 2:
Area-Proportional Venn Diagram of Initial and Secondary Vasopressor Utilization

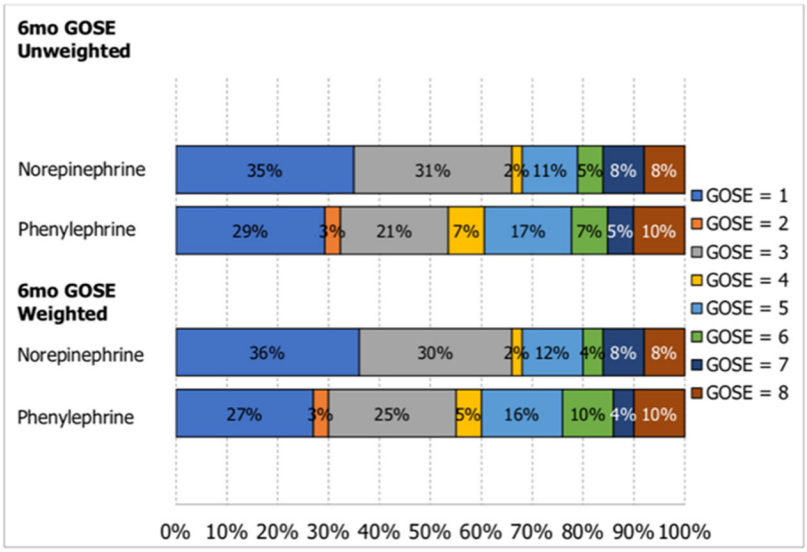


Figure 3:
GOSE distribution by initial vasopressor exposure

Table 1:

Study population demographic and clinical characteristics

Variable		First IV Vasopressor		
	Total	**Norepinephrine**	**Phenylephrine**	**Other**
Subjects	**156**	**79 (51%)**	**69 (44%)**	**8 (5%)**
Had Second Vasopressor Type				
No	85 (54%)	54 (64%)	27 (32%)	4 (5%)
Yes	71 (46%)	25 (35%)	42 (59%)	4 (6%)
Mean (SD) hours	27.8 (39.6)	33.4 (43.9)	26.5 (38.5)	6.6 (9.4)
0-4 hours	25 (16%)	6 (24%)	16 (64%)	3 (12%)
4-24 hours	26 (17%)	11 (42%)	14 (54%)	1 (4%)
24+ hours	20 (13%)	8 (40%)	12 (60%)	0 (0%)
Site				
A	37 (24%)	30 (81%)	5 (14%)	2 (5%)
B	7 (4%)	3 (43%)	4 (57%)	0 (0%)
C	31 (20%)	7 (23%)	24 (77%)	0 (0%)
D	12 (8%)	11 (92%)	1 (8%)	0 (0%)
E	39 (25%)	18 (46%)	19 (49%)	2 (5%)
F	1 (1%)	0 (0%)	1 (100%)	0 (0%)
G	9 (6%)	5 (56%)	3 (33%)	1 (11%)
H	2 (1%)	1 (50%)	1 (50%)	0 (0%)
I	4 (3%)	1 (25%)	3 (75%)	0 (0%)
J	1 (1%)	0 (0%)	0 (0%)	1 (100%)
K	1 (1%)	0 (0%)	1 (100%)	0 (0%)
L	1 (1%)	0 (0%)	0 (0%)	1 (100%)
M	11 (7%)	3 (27%)	7 (64%)	1 (9%)
Age				
Mean (SD)	43.1 (17.3)	43.3 (17.8)	43.1 (17.4)	41.8 (12.4)
<20	9 (6%)	6 (67%)	3 (33%)	0 (0%)
20-29	37 (24%)	17 (46%)	18 (49%)	2 (5%)
30-39	29 (19%)	16 (55%)	12 (41%)	1 (3%)
40-49	26 (17%)	12 (46%)	11 (42%)	3 (12%)
50-59	27 (17%)	11 (41%)	14 (52%)	2 (7%)
60-69	13 (8%)	9 (69%)	4 (31%)	0 (0%)
70-79	13 (8%)	7 (54%)	6 (46%)	0 (0%)
80+	2 (1%)	1 (50%)	1 (50%)	0 (0%)

Variable		First IV Vasopressor		
	Total	Norepinephrine	Phenylephrine	Other
Sex				
Male	121 (78%)	63 (52%)	53 (44%)	5 (4%)
Female	35 (22%)	16 (46%)	16 (46%)	3 (9%)
Race				
White	122 (81%)	60 (49%)	56 (46%)	6 (5%)
Black	15 (10%)	10 (67%)	5 (33%)	0 (0%)
Other	13 (9%)	6 (46%)	7 (54%)	0 (0%)
Unknown	6	3 (50%)	1 (17%)	2 (33%)
Hispanic				
No	123 (82%)	62 (50%)	57 (46%)	4 (3%)
Yes	27 (18%)	15 (56%)	10 (37%)	2 (7%)
Unknown	6	2 (33%)	2 (33%)	2 (33%)
Education Years				
Mean (SD)	12.7 (2.7)	12.3 (3.1)	13.2 (2.2)	11.1 (2.5)
Less than high school	31 (24%)	23 (74%)	5 (16%)	3 (10%)
High school only	48 (38%)	18 (38%)	27 (56%)	3 (6%)
Some college	22 (17%)	11 (50%)	10 (45%)	1 (5%)
4yr degree	19 (15%)	10 (53%)	9 (47%)	0 (0%)
Post-graduate	7 (6%)	3 (43%)	4 (57%)	0 (0%)
Unknown	29	14 (48%)	14 (48%)	1 (3%)
Injury Cause				
MVC[i] (occupant)	40 (26%)	22 (55%)	15 (38%)	3 (8%)
MCC[ii]	19 (12%)	10 (53%)	9 (47%)	0 (0%)
MVC (cyclist or pedestrian)	25 (16%)	10 (40%)	13 (52%)	2 (8%)
Fall	38 (24%)	16 (42%)	22 (58%)	0 (0%)
Assault	9 (6%)	8 (89%)	1 (11%)	0 (0%)
Other/Unknown	25 (16%)	13 (52%)	9 (36%)	3 (12%)
Injury Cause				
Acceleration/deceleration	80 (52%)	38 (48%)	38 (48%)	4 (5%)
Blow to head	45 (29%)	24 (53%)	19 (42%)	2 (4%)
Head against object	105 (68%)	54 (51%)	45 (43%)	6 (6%)
Crush	5 (3%)	1 (20%)	4 (80%)	0 (0%)
Blast	0 (0%)	---	---	---

Variable		First IV Vasopressor		
	Total	Norepinephrine	Phenylephrine	Other
Ground level fall	22 (14%)	10 (45%)	11 (50%)	1 (5%)
Fall from height	41 (26%)	20 (49%)	21 (51%)	0 (0%)
Gunshot	0 (0%)	---	---	---
Fragment	0 (0%)	---	---	---
Other	6 (4%)	1 (17%)	4 (67%)	1 (17%)
Unknown	1	1 (100%)	0 (0%)	0 (0%)
GCS ER Arrival				
Mean (SD)	5.0 (2.8)	5.0 (2.8)	5.2 (3.0)	3.9 (1.6)
Severe (3-8)	128 (82%)	66 (52%)	54 (42%)	8 (6%)
Moderate (9-12)	28 (18%)	13 (46%)	15 (54%)	0 (0%)
ISS Non-Head/Neck [iii]				
Mean (SD)	8.4 (9.2)	8.9 (10.3)	7.4 (7.6)	11.9 (9.7)
Unknown	3	0	2	1
AIS Head [iv]				
Mean (SD)	4.1 (1.1)	4.1 (1.0)	4.0 (1.3)	4.9 (0.4)
Unknown	3	0	2	1
ER SBP (mm Hg)				
Mean (SD)	140 (34)	141 (35)	139 (31)	135 (52)
Unknown	5	3	2	0
ER MAP (mm Hg)				
Mean (SD)	106 (26)	104 (27)	109 (25)	97 (30)
Unknown	23	8	15	0
ER Blood Transfusion				
No	117 (75%)	62 (53%)	48 (41%)	7 (6%)
Yes	38 (25%)	16 (42%)	21 (55%)	1 (3%)
Unknown	1	1 (100%)	0 (0%)	0 (0%)
Initial CT [v]				
Negative	2 (1%)	1 (50%)	1 (50%)	0 (0%)
Positive	140 (99%)	71 (51%)	64 (46%)	5 (4%)
Unknown	14	7 (50%)	4 (29%)	3 (21%)

Variable		First IV Vasopressor		
	Total	Norepinephrine	Phenylephrine	Other
Rotterdam Score				
Mean (SD)	3.7 (1.3)	3.7 (1.2)	3.6 (1.4)	4.4 (1.5)
2	22 (16%)	9 (41%)	13 (59%)	0 (0%)
3	55 (39%)	28 (51%)	25 (45%)	2 (4%)
4	22 (16%)	13 (59%)	8 (36%)	1 (5%)
5	23 (16%)	15 (65%)	8 (35%)	0 (0%)
6	18 (13%)	6 (33%)	10 (56%)	2 (11%)
Unknown	16	8 (50%)	5 (31%)	3 (19%)
History of Hypertension				
No	107 (76%)	53 (50%)	48 (45%)	6 (6%)
Yes	33 (24%)	16 (48%)	15 (45%)	2 (6%)
Unknown	16	10 (63%)	6 (38%)	0 (0%)
History of TIA [vi]				
No	140 (100%)	69 (49%)	63 (45%)	8 (6%)
Yes	0 (0%)	---	---	---
Unknown	16	10 (63%)	6 (38%)	0 (0%)
ER Mannitol or Hypersaline				
No	115 (74%)	63 (55%)	46 (40%)	6 (5%)
Yes	41 (26%)	16 (39%)	23 (56%)	2 (5%)
Placement of ICP Monitor [vii] (ED or first 24hrs)				
No	38 (24%)	15 (39%)	19 (50%)	4 (11%)
Yes	118 (76%)	64 (54%)	50 (42%)	4 (3%)
Mechanical Ventilation (ED or first 24hrs)				
No	12 (8%)	3 (25%)	6 (50%)	3 (25%)
Yes	144 (92%)	76 (53%)	63 (44%)	5 (3%)

[i] MVC = motor vehicle collision

[ii] MCC = motor cycle collision

[iii] ISS = Injury Severity Score

[iv] AIS = Abbreviated Injury Scale

[v] CT = Computed tomography

[vi] TIA = Transient ischemic attack

[vii] ICP = Intracranial pressure monitor

Table 2:

Association of initial vasopressor choice of norepinephrine (NE) or phenylephrine (PE) with primary and secondary outcomes

Outcomes		First IV Vasopressor		Unweighted		Weighted	
	Total	**Norepinephrine**	**Phenylephrine**	**Effect size**	**p**	**Effect size**	**p**
6-Month GOSE (1-8) [i]							
Data collected	120 (81%)	62 (78%)	58 (84%)	**OR**	**p**	**OR**	**p**
GOSE 1-4	77 (64%)	42 (68%)	35 (60%)	1.38 (0.65, 2.92)	.476	1.40 (0.66, 2.96)	.376
GOSE 5-8	43 (36%)	20 (32%)	23 (40%)				
Unknown	28	17	11				
6-Month DRS(0-29) [i]							
Data Collected	79 (53%)	38 (48%)	41 (59%)	**Estimate**	**p**	**Estimate**	**p**
Mean (SD)	6.1 (6.4)	6.3 (6.3)	5.9 (6.5)	−0.44 (−3.31, 2.43)	.762	−0.43 (−3.44, 2.58)	.776
Unknown	69	41	28				
Length of Hospital Stay [ii]				**HR**	**p**	**HR**	**p**
Mean (SE)	27.2 (1.7)	25.7 (2.3)	28.7 (2.6)	0.84 (0.58, 1.22)	.840	0.89 (0.62, 1.29)	.534
Length of ICU Stay [ii]				**HR**	**p**	**HR**	**p**
Mean (SE)	16.9 (1.2)	18.4 (1.6)	15.2 (1.6)	1.22 (0.84, 1.78)	.292	1.21 (0.83, 1.76)	.314
Discharged Alive [i]				**OR**	**p**	**OR**	**p**
No	32 (22%)	19 (24%)	13 (19%)	1.36 (0.62, 3.02)	.443	1.65 (0.73, 3.74)	.231
Yes	116 (78%)	60 (76%)	56 (81%)				
Required Dialysis [i]				**OR**	**p**	**OR**	**p**
No	142 (97%)	76 (96%)	66 (99%)	0.38 (0.04, 3.78)	.412	0.78 (0.13, 4.84)	.792
Yes	4 (3%)	3 (4%)	1 (1%)				
Unknown	2	0	2				

[i] Phenylephrine group was reference group for odds ratio, hazard ratio, or estimates

[ii] Deaths treated as censored observations