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Early vasopressor administration in pediatric blunt liver and spleen injury: An ATOMAC + study☆,☆☆,★

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ABSTRACT

Background: No prior studies have examined the outcomes of early vasopressor use in children sustaining blunt liver or spleen injury (BLSI).
Methods: A planned secondary analysis of vasopressor use from a 10-center, prospective study of 1004 children with BLSI. Inverse probability of treatment weighting (IPTW) was used to compare patients given vasopressors <48 h after injury to controls based on pretreatment factors. A logistic regression was utilized to assess survival associated with vasopressor initiation factors on mortality and nonoperative management (NOM) failure.
Results: Of 1004 patients with BLSI, 128 patients were hypotensive in the Pediatric Trauma Center Emergency Department (ED); 65 total patients received vasopressors. Hypotension treated with vasopressors was associated with a sevenfold increase in mortality (AOR = 7.6 [$p < 0.01$]). When excluding patients first given vasopressors for cardiac arrest, the risk of mortality increased to 11-fold (AOR = 11.4 [$p = 0.01$]). All deaths in patients receiving vasopressors occurred when started within the first 12 h after injury. Vasopressor administration at any time was not associated with NOM failure.
Conclusion: After propensity matching, early vasopressor use for hypotension in the ED was associated with an increased risk of death, but did not increase the risk of failure of NOM.
Level of evidence: Level III prognostic and epidemiological, prospective.

Traditionally, the early use of vasopressors to manage pediatric blunt liver and spleen injuries (BLSI) has been avoided owing to concerns of increased risk of bleeding or death. However, vasopressors are currently utilized to maintain cerebral perfusion in polytrauma patients with comorbid traumatic brain injury (TBI) [1]. Previous adult observational studies have shown that, independent of injury and clinical factors, early vasopressor use in traumatic injury is associated with higher short-term mortality rates [2,3]. Animal models of hemorrhagic shock in polytrauma also suggest that vasopressors used in excess and without associated fluid infusion may have deleterious effects [1]. One rationale for avoiding vasopressor use for hemorrhagic shock is concern for vasoconstriction reducing perfusion to end organs, such as the kidney. Sperry et al. [3] suggest that in adult patients who survive at least 48 h postinjury, vasopressor use within 24 h of blunt traumatic injury was associated with higher risk of mortality, should be used judiciously, and should not replace aggressive crystalloid resuscitation. By contrast, Beloncle et al. [1] claim that, for abdominal lesions, early vasopressor

Abbreviations: BLSI, blunt liver or spleen injury; NOM, nonoperative management.
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infusion leading to splanchnic vasoconstriction can potentially reduce hemorrhage from splanchnic vessels while allowing sufficient perfusion to other organs. The purpose of this study was to describe when and how vasopressors have been used in a multicenter pediatric BLSI prospective study, and assess the associated risks of early (within 48 h) vasopressor use in pediatric BLSI patients with and without comorbid TBI. We evaluated two main clinical outcomes: (1) mortality and (2) failure of nonoperative management (NOM) of liver and spleen injury owing to bleeding. To our knowledge, this is the first multicenter pediatric study to assess associated risks of vasopressor use in a pediatric (age 0–18) BLSI cohort of patients.

1. Methods

This study was a planned secondary analysis of vasopressor administration from a large multicenter prospective observational study. Subjects were 18 years or younger presenting to one of ten Level I pediatric trauma centers (PTC) in the ATOMAC + group [ATOMAC oringinally stood for Arizona Texas Oklahoma Memphis Arkansas Consortium]. Inclusion criteria required computed tomography (CT) evidence of BLSI between April 2013 and January 2016. Institutional Review Board approval was obtained at each institution. Participating centers included: Phoenix Children's Hospital (Phoenix, AZ), The Children's Hospital at OU Medical Center (Oklahoma City, OK), Children's Medical Center, part of Children's Health^{SM} (Dallas, TX), Le Bonheur Children's Hospital (Memphis, TN), Dell Children's Medical Center (Austin, TX), Arkansas Children's Hospital (Little Rock, AR), Children's Healthcare of Atlanta (Atlanta, GA), Mercy Children's Hospital (Kansas City, MO), Akron Children's Hospital (Akron, OH), and American Family Children's Hospital (Madison, WI). All sites had previously adopted the ATOMAC Blunt Pediatric Spleen/Liver Injury Guideline (v11.0) for NOM as a standard of care. The ATOMAC guideline did not specify clinical decision rules for the administration of vasopressors.

Demographic, injury, pretreatment, treatment, and clinical outcome variables were collected for all study subjects. These included prospective data on location of vasopressor use and clinical indications for initiation of the vasopressor. Data were collected and managed with REDCap (Research Electronic Data Capture), hosted at Phoenix Children's Hospital [4]. REDCap is a secure, Web-based application, compliant with federal regulatory requirements for health care data to facilitate data capture in multisite research studies.

Of 1004 eligible patients, there were 65 patients whose management for BLSI included vasopressors within the first 48 h of injury, and 939 patients whose management did not include vasopressors during the same period. Vasopressors were utilized in at least one patient within the first 48 h at 9 of the 10 trauma centers. In order to assess mortality and NOM for pediatric patients treated with vasopressors, we utilized inverse probability of treatment weighting (IPTW) to assign a weight to all 1004 patients in the cohort. This weight reflected how likely the patient was to be treated with a vasopressor based on baseline covariates. Timing of vasopressor administration was not considered as a covariate. The purpose of IPTW was to create a weighted sample that balances the pretreatment conditions between the treatment and the control subjects. A propensity score model was estimated for all 1004 subjects to generate the propensity scores (weights) using a generalized boosted regression (GBR) [5] method that is widely recognized as an unbiased method to ensure balance between the control and treatment group with a large number of covariates [5,6]. The propensity score is the probability of a subject receiving a vasopressor conditional on observed baseline covariates while the IPTW is the inverse of the probability of receiving the treatment the subject received. Weighting by the inverse probability results in a pseudosample where the baseline covariates for the subjects are independent of the treatment status [7]. Using IPTW ensures the control group is independent but is not different substantially from the treatment group for measured baseline covariates. IPTW scores were calculated using the R Toolkit for Weighting and Analysis of Nonequivalent Groups (*twang*) v1.5 [6]. This toolkit provides several balance metrics for IPTW via GBR (mean standardized bias, maximum standardized bias, mean Kolmogorov–Smirnov (KS), or maximum KS across the pretreatment covariates). Since all possible variables were included in model development, these metrics were used to select the optimal set of covariates to ensure balance in the distribution using differences in propensity scores between the two groups. Specific hemoglobin (Hb) and resuscitation volumes are not included because they did not improve model specificity.

Kaplan–Meier survival analysis was performed to identify mortality risk cut-points associated with the timing of vasopressor administration in each hour after injury. Fig. 1 shows the survival curve for the cumulative survival from timing of vasopressor administration. Kaplan–Meier results identified several potential cut-points for vasopressor timing risk (hours post injury): 1 h; 2.5 h; 5 h, 7 h and 12 h. These cut points were then assessed for sensitivity/specificity using receiver operating characteristic (ROC) curves. Only three timing cut-points optimized sensitivities and specificities. Sensitivities for immediate (<1 h); early (1.0–2.5); and late (>2.5) vasopressor administration were 81%, 74% and 61% respectively; specificities were respectively: 91%, 86% and 71%. To assess the timing of vasopressor administration on mortality and NOM, we constructed three binary timing variables of clinical relevance for vasopressor administration: immediate (<1 h from injury = 1, else = 0); early (1.0–2.5 h = 1, else = 0); and late (>2.5 h = 1, else = 0). Specific timing of vasopressor administration within the first 48 h was missing for 13 (20%) of 65 vasopressor patients. Statistically significant ORs from the bivariate regressions of mortality/NOM on demographic and clinical characteristics were used to select the final adjusted regression models assessing the associated risks of vasopressor timing. Since the covariate of interest was vasopressor timing, it is important to investigate confounders even after IPTW [8,9]; we estimated adjusted odds ratios (AOR) for vasopressor timing variables controlling for clinical conditions. All two-way interaction effects were also estimated; none were significant. (See Tables 1 and 2.)

All data analyses were conducted with R v3.4.2 (www.R-project.org) and the R *survey* package v3.35[8] in RStudio v1.1.383 (www.rstudio.com). Descriptive statistics, χ^2, Fisher exact test and Mann–Whitney U test statistics were computed where appropriate to assess clinical differences within the treatment cohort of 65 patients who received vasopressors. Confidence intervals were set at 95% and significance of all statistical tests was set at $P < 0.05$.

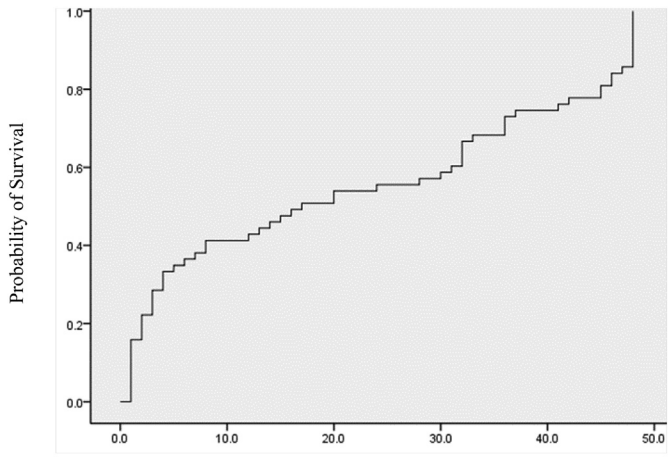

Fig. 1. Kaplan–Meier survival function for first vasopressor initiation (hours from injury).

Table 1
Unweighted and weighted demographics and clinical characteristics.

			Unweighted				IPTW			
	Vasopressor		Control				Control			
Covariate	***n* = 65**		***n* = 939**		**OR**	**(95% CI)**	***n* = 939**		**OR**	**(95% CI)**
	***n* (%)**		***n* (%)**				***n* (%)**			
Male	35	(54)	592	(63)	0.7	(0.4–1.2)	385	(41)	1.8	(0.8–4.0)
Severe GCS (≤8)	40	(62)	56	(6)	27.8***	(15.4–50.1)	498	(53)	1.4	(0.6–3.2)
Severe ISS (≥22)	56	(86)	441	(47)	12.3***	(4.9–31.0)	789	(84)	0.8	(0.3–2.2)
Massive transfusion protocol[a]	25	(38)	28	(3)	25.1***	(13.1–47.9)	263	(28)	1.7	(0.6–4.7)
Transfused	61	(94)	150	(16)	82.1***	(28.7–224.0)	826	(88)	1.9	(0.6–5.6)
Intubated in field	16	(25)	28	(3)	10.2***	(5.2–20.1)	207	(22)	1.1	(0.4–2.8)
Injured organ[b]										
Liver	30	(46)	469	(50)	0.2***	(0.1–0.3)	441	(47)	0.7	(0.3–1.7)
Spleen	10	(15)	394	(42)	0.1***	(0.0–0.2)	263	(28)	0.4	(0.1–1.2)
Both	25	(39)	75	(8)	1.1	(1.0–1.4)	235	(25)	0.1	(0.03–0.1)
Injury grade (>3)										
Spleen	14	(22)	122	(13)	1.8	(1.0–3.4)	178	(19)	1.3	(0.4–3.6)
Liver	23	(35)	113	(12)	3.7***	(2.2–6.5)	235	(25)	1.7	(0.7–4.2)
Kidney	2	(3)	28	(3)	1.0	(0.2–4.1)	28	(3)	1.0	(0.2–5.7)
Pancreas	1	(2)	2	(<1)	8.0	(0.7–89.9)	2	(<1)	20.5	(1.8–80.4)
Signs of instability at trauma assessment										
Tachycardia (HR > 100 bpm)	42	(65)	197	(21)	6.7***	(4.0–11.5)	648	(69)	0.8	(0.4–1.9)
Hypotension (SBP < 2× age + 55)	48	(74)	75	(8)	29.0***	(16.1–52.3)	648	(69)	1.3	(0.6–2.7)
Pallor	24	(37)	56	(6)	9.8***	(5.5–17.4)	263	(28)	1.5	(0.6–4.2)
Delayed capillary refill	26	(40)	28	(3)	20.9***	(11.3–38.9)	291	(31)	1.4	(0.5–4.0)
Cold extremities	23	(35)	19	(2)	22.8***	(11.7–44.2)	291	(31)	1.2	(0.4–3.3)
No response to fluid/blood	26	(40)	19	(2)	34.1***	(17.3–67.4)	263	(28)	1.7	(0.6–4.8)
Free fluid on ultrasound	14	(22)	47	(5)	5.0***	(2.6–9.6)	178	(19)	1.1	(0.4–3.4)
CT blush	12	(18)	47	(5)	4.7***	(2.3–9.5)	207	(22)	0.8	(0.2–2.7)
Additional injuries										
TBI	41	(63)	150	(16)	9.1***	(5.4–15.6)	554	(59)	1.1	(0.5–2.5)
Lung trauma	44	(68)	310	(33)	4.3***	(2.5–7.4)	648	(69)	0.9	(0.4–2.0)
Pelvic fracture	15	(23)	94	(10)	2.6**	(1.4–4.9)	263	(28)	0.7	(0.3–1.8)
Rib fracture	33	(51)	169	(18)	4.7***	(2.8–7.8)	441	(47)	1.2	(0.5–2.7)
Femur fracture	14	(22)	47	(5)	4.9***	(2.5–9.4)	291	(31)	0.6	(0.2–1.6)
Spinal cord injury	10	(15)	19	(2)	7.9***	(3.6–17.7)	122	(13)	1.1	(0.3–4.4)
Other extremity fracture	22	(34)	178	(19)	2.2**	(1.3–3.8)	385	(41)	0.7	(0.3–1.7)
Covariate	***n* = 65**	***n* = 939**	**OR**	**(95% CI)**		***n* = 939**	**OR**	**(95% CI)**		
	***n* (%)**	**n (%)**				***n* (%)**				
	Median [IQR]	**Median [IQR]**				**Median [IQR]**				
Mechanism of injury										
Fall	2	(3)	132	(14)	0.2*	(0.0–0.6)	28	(3)	1.4	(0.3–6.4)
MVC	39	(60)	300	(32)	3.1***	(1.9–5.2)	620	(66)	0.9	(0.4–1.9)
Pedestrian/cyclist struck	11	(17)	103	(11)	1.7	(0.8–3.2)	150	(16)	1.0	(0.4–2.6)
ATV	1	(2)	75	(8)	0.2	(0.0–0.8)	28	(3)	0.8	(0.1–6.3)
SNAT	7	(11)	47	(5)	2.8*	(1.2–5.9)	56	(6)	1.7	(0.6–4.9)
Bicycle (not vs. auto	0	(0)	66	(7)	0.0	N/A[c]	0	(0)	0.0	N/A[c]
Motorcycle	0	(0)	19	(2)	0.0	N/A[c]	0	(0)	0.0	N/A[c]
Sport related	0	(0)	85	(9)	0.0	N/A[c]	0	(0)	0.0	N/A[c]
Struck/crush injury	0	(0)	47	(5)	0.0	N/A[c]	0	(0)	0.0	N/A[c]
Assault	1	(2)	9	(1)	1.8	(0.1–10.0)	0	(0)	5.6	(0.4–7.0)
Other	4	(6)	47	(5)	1.2	(0.4–3.0)	56	(6)	1.2	(0.2–7.3)
Site										
PTC 1	12	(18)	131	(14)	1.3	(0.7–2.4)	122	(13)	1.4	(0.4–5.1)
PTC 2	13	(20)	103	(11)	2.1*	(1.0–3.8)	150	(16)	1.3	(0.4–3.9)
PTC 3	13	(20)	113	(12)	2.0*	(1.0–3.5)	235	(25)	0.8	(0.3–2.3)
PTC 4	6	(9)	113	(12)	0.7	(0.3–1.6)	85	(9)	1.5	(0.5–4.2)
PTC 5	6	(9)	113	(12)	0.8	(0.3–1.9)	150	(16)	0.6	(0.2–2.0)
PTC 6	3	(5)	103	(11)	0.4	(0.1–1.1)	85	(9)	0.5	(0.1–1.9)
PTC 7	3	(5)	47	(5)	0.9	(0.2–2.5)	28	(3)	1.8	(0.3–9.5)
PTC 8	0	(0)	56	(6)	0.0		0	(0)	0.0	
PTC 9	6	(9)	94	(10)	0.9	(0.3–2.0)	56	(6)	1.6	(0.4–6.1)
PTC 10	3	(5)	66	(7)	0.6	(0.2–1.7)	28	(3)	0.9	(0.3–3.5)
Age (years)	8.0	[6.0, 14.2]	10.4	[3.9, 13.8]	1.0	(0.9–1.0)	9.0	[5.3, 13.5]	1.0	(0.9–1.0)
Weight (kg)	30.0	[21.9, 59.0]	37.7	[16.0, 55.9]	1.0	(1.0–1.0)	33.1	[21.0, 52.9]	1.0	(1.0–1.0)

*p < 0.05; **p < 0.01; ***p < 0.001.
[a] Each site's MTP protocol was used to guide administration of blood products.
[b] All patients were treated for liver injury, spleen injury, or both. Some patients in addition to their liver and/or spleen injury may have a kidney and/or pancreas injury.
[c] Unable to estimate OR or CI owing to lack of covariate data in the vasopressor group.

2. Results

During the study period 1004 eligible study subjects were included. There were 240 patients with hypotension, defined as systolic blood pressure (SBP) < [(2 × patient age) + 55] at any time within the first 48 h from injury; 128 with hypotension in the PTC Emergency Department (ED). The median patient age was 10.3 [5.9, 14.2] years old; 61.9% of patients were male. Of the 128 who were hypotensive in the ED, 65 received vassopressors. A massive transfusion protocol (MTP) provided guidelines to administer blood products. In total, 61 patients

Table 2
First vasopressor initiation characteristics.

Location first vasopressor initiated	Code dose bolus ($n = 20$)	Vasopressor drip ($n = 32$)	First vasopressor (n)	Supporting clinical features (n)	Mortality rate
Prehospital ($n = 8$)	8	0	Epinephrine – CDB (8)	Bradycardia (1) Cardiac arrest (7) Hypotension 2° brain injury (1) Hypotension 2° spinal cord injury (1)	75%
OSH ED ($n = 5$)	3	2	Dopamine ≥5 μg/kg/min (3) Epinephrine – CDB (2)	Cardiac arrest (1) Hypotension 2° blood loss (3) Hypotension 2° brain injury (2)	60%
Interfacility transport ($n = 3$)	2	1	Epinephrine – CDB (1) Epinephrine – VD (1) Phenylephrine – CDB (1)	Hypotension 2° blood loss (3) Cannot determine (1)	33%
PTC ED ($n = 10$)	4	6	Dopamine ≥5 μg/kg/min (1) Epinephrine – CDB (4) Epinephrine – VD (4) Norepinephrine (1)	Bradycardia (4) Cardiac arrest (4) Hypotension 2° blood loss (7) Hypotension 2° brain injury (2)	50%
OR ($n = 5$)	3	2	Dopamine ≥5 μg/kg/min (2) Phenylephrine – CDB (3)	Hypotension 2° blood loss (4) Hypotension 2° brain injury (1) Cannot determine (1)	0%
CT ($n = 2$)	1	1	Epinephrine – CDB (1) Epinephrine – VD (1)	Hypotension 2° blood loss (2)	0%
PICU ($n = 19$)	0	19	Dopamine <5 μg/kg/min (1) Dopamine ≥5 μg/kg/min (6) Epinephrine – VD (7) Norepinephrine (2) Phenylephrine – VD (1) Vasopressin (2)	Hypotension 2° blood loss (14) Hypotension 2° brain injury (9) Hypotension 2° spinal cord injury (2) Cannot determine (2)	21%

CDB = code-dose bolus; VD = vasopressor drip.

were transfused and MTP was followed for 25 patients. Twenty-five patients died and 37 patients failed NOM for bleeding.

2.1. Vasopressor first administration location and timing

Of the 65 who received vassopressors, 52 had data describing the location and manner of vasopressor administration. For these 52 vasopressor patients, the highest mortality rate occurred for initiation of vassopressors prehospital and the lowest mortality rate is for initiation during Computed Tomography (CT) or in the operating room (OR). For 38% (20/52) of patients, the first vasopressor administration was via code-dose bolus; for 62% (32/52) of patients, first administration was via vasopressor drip. Code-bolus was more likely to have been administered prehospital; vasopressor drip in the pediatric intensive care unit (PICU); otherwise there were no significant differences in administration method associated with the location of patient in the first 48 h. Epinephrine was the most common vasopressor first initiated, accounting for 56% (29/52) of patients. The median [IQR] for time of vasopressor initiation (in hours) from injury was 3.0 [1.1, 7.6] h. The difference between median time (in hours) of initial vasopressor administration for patients who died (1.4 [0.5, 3.3]) and patients who survived (5.0 [2.5, 12.6]) was statistically significant (Mann–Whitney U = 354, p = 0.003).

2.2. Vasopressor administration, mortality and NOM failure

Adjusted odds ratios for mortality and NOM failure are given in Table 3. After controlling for confounding risk factors, first vasopressor administration at any time during the first 48 h increased the odds of mortality more than seven times (AOR = 7.6 [p = 0.025]). The only other clinical risk factors associated with mortality were hypotension in the PTC ED (AOR = 16.9 [p < 0.001]) and GCS < 8 at the first ED where patient presented (AOR = 6.1 [p = 0.02]); patient weight was marginally protective (AOR = 0.98 [p = 0.034]). Table 3 also shows vasopressor use was not a significant risk factor for NOM failure (AOR = 1.9 [p = 0.58]); spleen injury grade > 3 (AOR = 7.4[p = 0.007]) and whether MTP was initiated (AOR = 6.1 [p = 0.03]) were associated risk factors for NOM failure.

2.3. Timing of vasopressor administration, mortality and NOM failure

We estimated three models for mortality using three mutually exclusive binary time-binned vasopressor administration indicator variables (Table 4). Hypotension in the PTC ED was associated with a 14 to 33-fold increase in mortality risk depending on time of administration. Vasopressor administered < one hour after injury was a significant independent risk factor for mortality (AOR = 12.9 [p = 0.02]). Hypotension in the PTC ED (AOR = 32.7 [p = 0.001]) was the only other clinical risk factor independently associated with mortality when

Table 3
Adjusted odds ratios and predicting mortality and NOM failure.

	Clinical outcome	
	Mortality $N = 906$	NOM failure $N = 960$
Risk factor	AOR (95% CI)	AOR (95% CI)
Vasopressor at any time within 48 h	7.6* (1.3–44.5)	1.9 (0.2–20.4)
1st vasopressor given for cardiac arrest	2.3 (0.3–19.1)	*Not included*
1st vasopressor given for hypotension 2° blood loss	0.4 (0.1—2.7)	5.2 (0.9–31.8)
GCS ≤8	6.1* (1.3–28.6)	*Not included*
Hypotensive in PTC ED (SBP < 2× age + 55)	16.9*** (3.4–84.2)	*Not included*
Delayed capillary refill	*Not included*	1.3 (0.4–4.4)
Free fluid on ultrasound	*Not included*	3.1 (0.6–16.8)
Field intubation	2.9 (0.5–15.9)	*Not included*
MTP[a]	2.7 (0.6–12.7)	6.1* (1.3–30.0)
TBI	*Not included*	0.2 (0.1–1.2)
Spleen grade > 3	*Not included*	7.4** (1.7–31.6)
Kidney grade > 3	1.6 (0.3–8.5)	0.2 (0.01–4.2)
Liver grade > 3	*Not included*	1.9 (0.39–8.9)
Male	5.8 (0.98–33.5)	*Not included*
Weight	0.98* (0.95–1.0)	*Not included*
(Intercept)	0.001 (0.0001–0.01)	0.02 (0.003–0.2)

*p < 0.05; **p < 0.01; ***p < 0.001.
GCS = Glasgow Coma Scale; PTC = pediatric trauma center; TBI = traumatic brain injury; MTP = massive transfusion protocol.
Not included: these factors were not included in the multivariate adjusted model based on statistically nonsignificant results from the unadjusted bivariate models.
[a] Each site's MTP protocol was used to guide administration of blood products.

Table 4
Adjusted odds ratios predicting mortality for immediate, early and late vasopressor administration within a 48 h period from injury.

Risk factor	Mortality $N = 906$		
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Vasopressor timing			
<1 h	12.9* (1.5–109.5)	--	--
1–2.5 h.	--	0.9 (0.002–4.8)	--
>2.5 h.	--	--	6.4 (0.8–51.2)
1st vasopressor given for cardiac arrest	0.8 (0.1–5.1)	6.4 (0.6–70.8)	11.7* (1.4–100.1)
1st vasopressor given for hypotension 2° to blood loss	0.8 (0.2–3.4)	1.6 (0.4–7.1)	0.7 (0.1–5.0)
GCS ≤ 8	6.9 (0.9–50.8)	6.8* (1.3–35.3)	9.7* (1.7–56.7)
Field intubation	2.9 (0.5–16.5)	1.7 (0.3–11.0)	1.8 (0.4–8.2)
Hypotensive in PTC ED (SBP < 2× age + 55)	32.7*** (5.3–203.1)	31.3*** (5.7–173.1)	14.2*** (3.3–63.3)
MTP[a]	1.7 (0.4–7.5)	3.1 (0.7–14.2)	2.7* (0.8–9.2)
Kidney grade > 3	0.8 (0.1–8.4)	0.6 (0.1–4.2)	1.3 (0.2–7.7)
Male	7.2* (1.0–51.3)	9.1* (1.1–76.3)	8.3* (1.2–58.0)
Weight	0.96* (0.9–1.0)	0.97 (0.9–1.0)	0.98 (0.96–1.0)
(Intercept)	0.002 (0.0001–0.02)	0.001 (0.001–0.11)	0.001 (0.000–0.1)

*p < 0.05; **p < 0.01; ***p < 0.001.
GCS = Glasgow Coma Scale; MTP = massive transfusion protocol.
[a] Each site's MTP protocol was used to guide administration of blood products.

accounting for vasopressors administered in the first hour. Hypotension in the PTC ED was also independently associated with mortality when accounting for vasopressors that were administered from 1 to 2.5 h (AOR = 31.3 [p = 0.001]) and >2.5 h (14.2 [p = 0.001]). Glasgow Coma Score (GCS) < 8 in the first ED was a risk factor independently associated with mortality when accounting for vasopressors administered from 1 to 2.5 h (AOR = 6.8 [p = 0.02]) and >2.5 h (AOR = 9.7 [p = 0.01]). First vasopressor initiation owing to cardiac arrest was significant when accounting for vasopressors that were administered >2.5 h (AOR = 11.7 [p = 0.02]). No patient died whose first vasopressor was initiated later than 12 h postinjury. Hypotension secondary to blood loss as the clinical indication for first vasopressor administration was an independent risk factor for NOM failure after we controlled for time to administration: < one hour (AOR = 7.5 [p = 0.01]); 1 to 2.5 h (AOR = 6.3 [p = 0.02]); > 2.5 h (AOR = 14.4 [p = 0.001]).

3. Discussion

3.1. Timing of first administration of vasopressors

A recent systematic review of adult patients with blunt or penetrating trauma found vasopressor use from prehospital through the ED was associated with an increased risk of short-term mortality [2]. Similar to previous research [2], we found vasopressor use in general (within 48 h of injury) in a cohort of pediatric BLSI patients was associated with mortality, increasing the risk over 7 times when compared to a propensity-matched cohort of patients where vasopressors were not administered, even after adjusting for clinical conditions such as blood loss, hypotension, severe TBI and cardiac arrest. This risk appears to be driven almost exclusively by patients who received vasopressors immediately after injury (<1 h). By contrast, there was no associated risk for patients who received vasopressors within 1–2.5 h from injury or later (2.6–126 h).

3.2. Location and first administration of vasopressors

Neither location nor delivery method altered the risk of mortality when controlling for time to first initiation suggesting that earlier administration carries the risk based on underlying clinical conditions. Although the PICU was the most common location for first administration, PICU had a low associated mortality rate and initiation in PICU was more commonly related to hypotension. Vasopressors were rarely initiated in the operating room (OR) or computed tomography (CT) and no patients with first initiation in these locations died.

3.3. Cardiac arrest

Cardiac arrest is a comorbidity of BLSI patients with prehospital administration of vasopressors [10,11] and often a precursor to mortality [12]. Similar to Van Haren et al. [10], when we controlled for cardiac arrest, vasopressor administration was associated with an eleven-fold increase in mortality risk (AOR = 11.4 [p = 0.01; CI 95%: 1.7–75.5]) when we excluded patients with cardiac arrest. We also found that a mortality risk of vasopressors was limited to the first hour after injury. In addition, vasopressor administration >2.5 h from injury owing to cardiac arrest *was* significant. In terms of timing, these results suggest a qualitative difference in risk between first vasopressor initiation after 2.5 h and first initiation owing to cardiac arrest.

3.4. Hypotension

Similar to Plurad et al. [9] our results suggest that the mortality risks associated with vasopressor use are not solely driven by cardiac arrest. In our study, hypotension secondary to blood loss was the only clinical feature supporting initial vasopressor administration that was protective for mortality but only for vasopressor initiation after the first hour (AOR = 0.52; 95% CI: 0.12–2.26; P = 0.37). Later administration of vasopressors in the course of patient treatment did not change the risk of mortality. These results are somewhat at odds with the suggestion by Beloncle et al. [1] that patients with an early death may have benefitted from early vasopressor use to manage hemorrhagic shock. We found that patients with fatal injuries were more likely to receive vasopressors earlier but not necessarily benefit from them. Seven of eight patients who received prehospital vasopressors underwent cardiac arrest and 6 of those patients died. Patients who were started on vasopressors for blood loss and lived were actually started later.

3.5. Traumatic brain injury

Vasopressors may reduce the risk of secondary brain injury in hypotensive TBI patients by increasing cerebral perfusion and mitigating elevated intracranial pressure (ICP) [11,13]. In our study, severe TBI was associated with most patient deaths, regardless of vasopressor use. Use of vasopressors in complex trauma patients presenting with combined severe BLSI and severe TBI may not benefit the patients as described in previous research. Animal studies have suggested that the use of epinephrine during cardiac arrest lowers cerebral perfusion in the postresuscitative phase. In our study, GCS ≤ 8 was an independent risk for mortality early after BLSI; after 2.5 h, there was no longer an independent risk associated with mortality for GCS ≤ 8. This result suggests that cardiac arrest,

intubation in the field, hemodynamic instability, and severe organ injury may be a risk constellation where vasopressors may not benefit the patient in the first few hours after injury with or without TBI.

3.6. NOM failure

Vasopressor initiation in pediatric BLSI patients did not independently increase the risk of subsequent NOM failure. For patients who received vasopressors *and* failed NOM ($n = 18$), 10 patients received a vasopressor prior to surgery and six (60%) died. All six failed NOM within five hours of injury and the median time to vasopressor initiation was 1.4 h after injury. Of the eight patients who received vasopressors during or after surgery, all survived. Although vasopressor initiation before abdominal surgery was associated with an increased risk of death, this result may also be an indication of associated underresuscitation. More research is needed to better isolate the risks of vasopressors from the risk of under resuscitation.

Later use in the operating room or PICU does not seem to be associated with increased risk of death or of failure of NOM.

4. Limitations

Despite being a large multicenter trial with 1004 patients, a limitation of this study was the relatively small size of the subpopulation of pediatric BLSI patients who were hypotensive ($n = 240$, 24%) or received vasopressors within 48 h of injury ($n = 65$, 6%). In addition to a small treatment cohort, patients who received vasopressors had more severe injuries, experienced more polytrauma and were at higher risk for cardiac arrest than typical BLSI patients. Although the GBR methodology optimizes assigned weighting given a small treatment cohort and a large number of pre-treatment conditions, rare clinical conditions and rare combinations of clinical conditions may have limited generalization beyond these data.

One strength of the study was the use of a 10-center prospective study where all 10 sites followed a strict NOM algorithm, providing some control over site variation in assessing clinical conditions such as hypotension and following guidelines for the management of clinical conditions. The centers relied on the use of ATLS and the ATOMAC algorithm for resuscitation. Vasopressors are not included in either of these for SOI management, so the providers were using the vasopressors outside these recommendations. We have not controlled for any extant site variation in those practices which may have confounded our results and limited generalization.

Another strength was the prospective collection of vasopressor data and data describing the timing and purpose for vasopressor initiation. We also accounted for any pretreatment differences between our treatment and control cohorts with IPTW via GBR. GBR is widely recognized as a robust estimation method that mitigates omitted variable bias and works well with small samples by stabilizing variance differences between the treatment and control cohorts so that outliers are managed more efficiently to ensure balance.[5] A final major strength of our study was the specific focus on the use of vasopressors in the pediatric BLSI population; to our knowledge, there have been no previous studies to date on vasopressors in the pediatric trauma population.

5. Conclusions

In a 10-center multisite prospective study using a propensity-matched control group, early use of vasopressors for hypotension was associated with an increased risk of mortality in severely injured children. Use of vasopressors after arrival to the pediatric trauma center also increased the risk of death, but abated for vasopressors used in the operating room or pediatric intensive care unit. Vasopressors use did not increase the risk of NOM failure.

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