The American Journal of Surgery 220 (2020) 1498–1502

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Southwestern Surgical Congress

Vasopressors in traumatic brain injury: Quantifying their effect on mortality

Navpreet K. Dhillon, Raymond Huang, Russell Mason, Nicolas Melo, Daniel R. Margulies, Eric J. Ley, Galinos Barmparas*

Department of Surgery, Division of Trauma and Critical Care, Cedars-Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 27 March 2020
Received in revised form
3 August 2020
Accepted 14 September 2020

Keywords:
Cerebral perfusion pressure
Hypotension
Trauma
Traumatic brain injury
Vasopressors

ABSTRACT

Background: The benefits of vasopressor (VP) use to improve clinical outcomes in traumatic brain injury (TBI) is unknown. We sought to characterize the use of VP in TBI patients and evaluate its impact on mortality.

Methods: A retrospective review was conducted of all TBI patients admitted to an ICU at a Level I trauma center from January 2014 to August 2016. Patients who had any VP administered (VP+) were compared to those who did not (VP-).

Results: Among the 556 patients analyzed, 83 (14.9%) received VP. The overall mortality was 9.2%, significantly higher in the VP + cohort (42.2% vs. 3.4%, $p < 0.01$). After adjusting for confounding factors, VP + patients had a significantly higher risk for in-hospital mortality (Adjusted Hazard Ratio: 2.77, adjusted $p = 0.01$).

Conclusion: Although VP may be temporarily useful in avoiding secondary insult to the brain in TBI patients, their use is not associated with improved survival.

Introduction

Preventing secondary brain insult remains the underlying principle on which the medical management of patients who have sustained a traumatic brain injury (TBI) is based upon.[1] This is accomplished by mainly avoiding hypoxia and hypotension. The Brain Trauma Foundation guidelines recommend maintaining a systolic blood pressure (SBP) of at least 100 mmHg for patients between the ages of 50–69, and above 110 mmHg for patients who are younger or older than this age group. Coupled with this, there are recommendations to target cerebral perfusion pressures (CPP) between 60 and 70 mmHg.[2] Adjuncts, such as vasopressors (VP), may be used to avoid hypotension and to promote adequate CPP, and consequently these agents are being used in daily clinical practice.[3]

Considering that the excess intrinsic catecholamine release in TBI patients may be associated with increased mortality, one would expect that the administration of certain, catecholaminergic VPs may have a similar effect on outcomes.[4,5] This however, conflicts with the common use of these agents in this setting, which is intended for improving CPP, preventing secondary injury to the brain, and improving survival. Certain vasopressors can theoretically increase brain tissue oxygenation as well.[6] The objective of this study was to characterize the use of VP in TBI patients and to evaluate their association with mortality. We hypothesized that VP use would be associated with increased mortality.

Material and methods

Study design and institutional practices

A retrospective review was conducted of all TBI patients admitted to an intensive care unit (ICU) at an academic, urban, Level I trauma center from January 2014 to August 2016. Patients with TBI were admitted either to the surgical ICU in the event of polytrauma, or to the neurosurgical ICU if injuries were predominantly involving the head, face, or spine. The ultimate decision to admit a patient to either ICU is always at the discretion of the trauma surgeon. Both neurosurgical and neurocritical care consultations are obtained at the time of admission to either ICU. No set

* Corresponding author. FACS, Surgery Cedars-Sinai Medical Center, Department of Surgery Division of Acute Care Surgery and Surgical Critical Care, 8635 West 3rd Street, Suite 650W, Los Angeles, CA, 90048, USA.

E-mail addresses: Navpreet.Dhillon@cshs.org (N.K. Dhillon), Raymond.Huang@cshs.org (R. Huang), Russell.Mason@cshs.org (R. Mason), Nicolas.Melo@cshs.org (N. Melo), Daniel.Margulies@cshs.org (D.R. Margulies), Eric.Ley@cshs.org (E.J. Ley), gbarmparas@gmail.com (G. Barmparas).

https://doi.org/10.1016/j.amjsurg.2020.09.016
0002-9610/

protocol existed for VP use; the decision of when to initiate VP use and with which agent was at the discretion of the rounding intensivist.

Data collection

Data collection included patient demographics, co-morbidities, mechanism of injury (blunt versus penetrating), Glasgow Coma Scale (GCS), vital signs on admission, laboratory studies obtained on admission, injury characteristics, and type of TBI on initial imaging (classified as contusion, intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), subdural hematoma (SDH), epidural hematoma (EDH), diffuse axonal injury (DAI), herniation, and/or other). Injury severity score (ISS) and regional abbreviated injury scale (AIS) scores for head/neck, chest, abdomen/pelvis, and extremities were obtained from the trauma registry.

The electronic medical record was queried for TBI-related procedures performed including craniectomy, craniotomy, external ventricular drain (EVD) placement, intracranial pressure (ICP) monitoring device placement, as well as need for additional interventions such as angioembolization, intubation, laparotomy, a maxillofacial operation, an orthopedic operation, and/or a spinal intervention. Administration of any VP, including dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, and/or vasopressin during the ICU stay was collected. Echocardiogram reports were reviewed for the ejection fraction (EF), the presence of wall motion abnormality, and hyperdynamic changes to the heart.

Outcomes data included ICU and hospital length of stay, ventilator days, and in-hospital mortality.

Analysis

Patients who received any VP (VP + cohort) during their ICU admission were compared to those who did not (VP-). Data are summarized as percentages for categorical variables and means with standard deviations (SD) or medians with interquartile range (IQR) for continuous variables. Categorical variables were compared using Pearson χ 2 or Fisher's exact test whereas comparisons of continuous variables were conducted using a Student's *t*-test or Mann-Whitney *U* Test, where appropriate. A *p* value of <0.05 was considered statistically significant. A Kaplan-Meier curve was generated and a Cox regression model with a time-dependent variable was utilized to adjust for differences between the two groups and to quantify the risk of VP use on mortality, accounting for the timing of initiation of VPs.

All statistical analyses were performed using IBM SPSS statistics for Windows, version 25 (IBM Corp. Armonk, N.Y, USA). This study was approved by the Institutional Review Board and the requirement for informed consent was waived.

Results

There were 556 patients that met inclusion criteria over the 32-month study period, of whom, 83 (14.9%) received VP (VP+). The most commonly used VP was norepinephrine (75.9%), followed by phenylephrine (56.6%), and vasopressin (28.9%) (Fig. 1). The median interval from admission to initiation of VPs was 1 day and the median duration of VP use was 2 days. VP + patients were significantly younger (54.3 ± 21.1 vs. 59.7 ± 23.2 years, p = 0.04) and more likely to have congestive heart failure (CHF) (7.2% vs. 2.7%, p < 0.01) (Table 1). VP+ were more likely to present with a SBP less than 90 mmHg (8.4% vs. 1.5%, p < 0.01) and be tachycardic with a heart rate over 100 bpm (44.6% vs. 23.3%, p < 0.01). They also had a significantly lower GCS (7.9 ± 4.9 vs. 13.4 ± 2.8, p < 0.01) and were more severely injured overall (ISS of 28.2 ± 12.2 vs. 17.9 ± 7.0, p < 0.01), as well as regionally in the head/neck, chest, abdomen/pelvis, and the extremities (Table 1). VP + patients additionally had a significantly lower Hgb (12.1 ± 2.0 vs. 13.0 ± 2.0, p < 0.01) and pH values (7.31 ± 0.14 vs. 7.36 ± 0.11, p < 0.01) on admission, while lactate levels were higher (4.4 ± 3.0 vs. 3.0 ± 1.7, p = 0.03). The type of TBI seen on initial imaging was similar among both cohorts with the exception of an EDH and/or herniation, which were seen more frequently in the VP + cohort (14.5% vs. 7.6%, p = 0.04, p < 0.01 and 2.4% vs. 0%, p < 0.01, respectively).

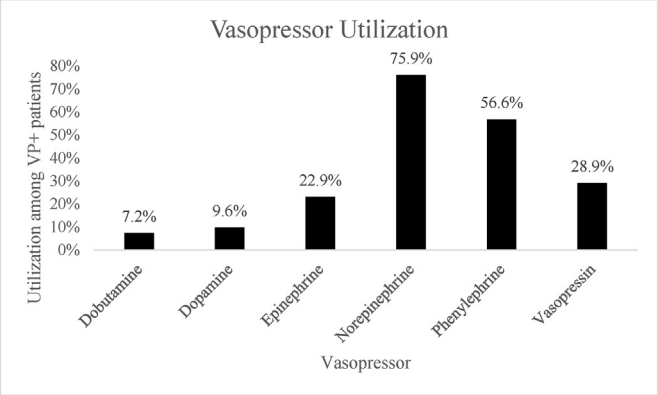

Fig. 1. Vasopressor utilization.

VP + patients were more likely to develop diabetes insipidus (2.4% vs. 0%, p = 0.02) and cerebral salt wasting (3.6% vs. 0%, p < 0.01). This cohort was also more likely to require surgical interventions and/or procedures related to their TBI, such as a craniectomy (16.9% vs. 1.9%, p < 0.01), EVD placement (10.8% vs. 3.4%, p < 0.01), or placement of an ICP monitoring device (21.7% vs. 1.3%, p < 0.01) (Table 2). More patients in the VP + cohort had an echocardiogram performed (57.8% vs. 28.5%, p < 0.01). Although the EF was similar on the echocardiogram, the presence of either wall motion abnormality (31.3% vs. 12.6%, p < 0.01) or hyperdynamic changes (25.0% vs. 15.6%, p < 0.01) were more likely to be reported for VP + patients.

The overall mortality was 9.2% (Table 3) and in the VP + patients, it increased in a stepwise fashion with the addition of each VP, to reach 100.0% for patients who received five or more VPs (Fig. 2). Fig. 3 depicts a Kaplan-Meier curve in which VP + patients had a significantly higher mortality (log rank p = 0.03). In a Cox regression model with a time-dependent variable accounting for the timing of initiation of VP, and adjusting for age, GCS, SBP on admission, ISS, pH on admission, presence of an EDH and herniation, and development of diabetes insipidus and cerebral salt wasting, VP + patients had a significantly higher risk for in-hospital mortality (Adjusted Hazard Ratio: 2.77; 95% CI: 1.24–6.77, adjusted p = 0.01).

Discussion

In TBI patients admitted to the ICU, the use of VP is common and the addition of each is associated with a stepwise increase in mortality. Patients in whom VP were utilized had more severe TBI and required TBI-related interventions more frequently. Overall, and when accounting for the timing of VP initiation in relation to admission, VP use was associated with a significantly higher risk for mortality.

Patients requiring VP appeared to be inherently different from those that did not. We found that VP patients were more frequently hemodynamically unstable at admission and had a more severe TBI and overall injury burden. Patients presenting with these characteristics following trauma typically have a worse prognosis.[7] Thus,

Table 1
Comparison of VP+ and VP- patients with respect to baseline characteristics and injury profile.

	Total (n = 556)	VP (+) (n = 83)	VP (−) (n = 473)	p value
Demographics				
- Age, y	58.9 ± 23.0	54.3 ± 21.1	59.7 ± 23.2	0.04
	60 (40–79)	52 (39–73)	62 (40–80)	
- Male, % (n)	64.9% (361)	71.1% (59)	63.8% (302)	0.20
Co-morbidities				
- CHF, % (n)	3.4% (19)	7.2% (6)	2.7% (13)	<0.01
- CKD, % (n)	2.5% (14)	4.8% (4)	2.1% (10)	0.14
- Diabetes, % (n)	10.8% (60)	9.6% (8)	11.0% (52)	0.71
- Alcoholic Cirrhosis, % (n)	10.8% (60)	10.8% (9)	10.8% (51)	0.99
- HTN, % (n)	30.6% (170)	21.6% (18)	32.1% (152)	0.06
Injury characteristics and hemodynamics				
- Blunt Trauma, % (n)	99.6% (554)	98.8% (82)	99.8% (472)	0.28
- SBP (mmHg)	140.2 ± 29.0	133.9 ± 38.3	141.3 ± 26.9	0.11
	139.5 (122–157)	136 (110–161)	140 (122–156)	
- SBP < 90 mmHg, % (n)	2.5% (14)	8.4% (7)	1.5% (7)	<0.01
- SBP < 60 mmHg, % (n)	0.5% (3)	2.4% (2)	0.2% (1)	0.01
- HR (bpm)	91.3 ± 23.3	99.6 ± 30.1	89.9 ± 21.6	<0.01
	88 (76–104)	97 (78–120)	87 (76–101)	
- HR > 100 bpm, % (n)	26.4% (147)	44.6% (37)	23.3% (110)	<0.01
- GCS	12.6 ± 3.7	7.9 ± 4.9	13.4 ± 2.8	<0.01
	14 (12–15)	7 (3–13)	14 (14–15)	
- ISS	19.5 ± 8.8	28.2 ± 12.2	17.9 ± 7.0	<0.01
	17 (14–25)	26 (18–34)	17 (13–21.5)	
- AIS Head/Neck	3.8 ± 0.7	4.4 ± 0.7	3.7 ± 0.6	<0.01
	4 (3–4)	5 (4–5)	4 (3–4)	
- AIS Chest	0.5 ± 1.1	1.1 ± 1.5	0.4 ± 1.0	<0.01
	0 (0–0)	0 (0–3)	0 (0–0)	
- AIS Abdomen/Pelvis	0.2 ± 0.8	0.6 ± 1.2	0.2 ± 0.7	<0.01
	0 (0–0)	0 (0–0)	0 (0–0)	
- AIS Extremity	0.5 ± 1.1	0.9 ± 1.4	0.5 ± 1.0	<0.01
	0 (0–0)	0 (0–2)	0 (0–0)	
Admission laboratory values				
- First Hg, g/dL	12.9 ± 2.0	12.1 ± 2.0	13.0 ± 2.0	<0.01
	13.9 (11.7–14.2)	12.2 (10.7–13.6)	13.1 (11.8–14.3)	
- First lactate, mmol/L	3.6 ± 2.5	4.4 ± 3.0	3.0 ± 1.7	0.03
	2.9 (1.9–4.5)	3.5 (2.4–5.5)	2.6 (1.7–4.1)	
- First pH	7.34 ± 0.13	7.31 ± 0.14	7.36 ± 0.11	<0.01
	7.36 (7.30–7.42)	7.34 (7.23–7.41)	7.38 (7.32–7.42)	
Type of TBI				
- Contusion, % (n)	17.1% (95)	12.0% (10)	18.0% (85)	0.19
- EDH, % (n)	8.6% (48)	14.5% (12)	7.6% (36)	0.04
- SDH, % (n)	57.0% (317)	66.2% (55)	55.4% (262)	0.07
- SAH, % (n)	45.7% (254)	53.0% (44)	44.4% (210)	0.15
- IPH, % (n)	6.5% (36)	3.6% (3)	7.0% (33)	0.25
- Herniation, % (n)	0.4% (2)	2.4% (2)	0.0% (0)	0.02
- DAI, % (n)	0.2% (1)	0.0% (0)	0.2% (1)	>0.99
- Other, % (n)	1.8% (10)	1.2% (1)	1.9% (9)	>0.99

Continuous values are reported as means ± standard deviation (SD), median (interquartile ranges), unless otherwise specified.
AIS, abbreviated injury score; CHF, congestive heart failure; CKD, chronic kidney disease; DAI, diffuse axonal injury; EDH, epidural hematoma; GCS, Glasgow Coma Scale; Hg, hemoglobin; HR, heart rate; HTN, hypertension; IPH, intraparenchymal hemorrhage; ISS, injury severity scale; SBP, systolic blood pressure; SAH, subarachnoid hemorrhage; SDH, subdural hematoma

one may assume that VP use could act as a surrogate for injury severity that fails to respond to conventional resuscitation measures. Despite using VP as a resuscitative adjunct, which may have occurred in certain cases, VP use did seem to extend a survival benefit. The findings from this study do not advocate for accepting hypotension in TBI patients to avoid the use of VP which potentially allow for improved cerebral perfusion; rather the objective of this study was to quantify the effect of VP use with respect to mortality. We cannot make further comments about how to best address hypotension in this patient cohort without additional investigation.

Several of the VP agents utilized in this study were catecholaminergic in nature. The central catecholamine surge after brain injury has been well described,[8,9] and it is known to lead to neuronal death, inflammation, and apoptosis.[10] Systemic rises in catecholamines also have a detrimental impact on cardiovascular physiology[11] and may elicit a systemic inflammatory response,[12] which some have implicated as mechanisms by which patients develop an overall deteriorated physiologic state, leading to poor outcomes.

The use of beta blockers, which act to suppress the effects of this innate catecholamine surge has been associated with decreased mortality in critically ill patients with TBI as shown in one multicenter, prospective study.[13] Practice management guidelines by the Eastern Association for the Surgery of Trauma conditionally recommend use of in-hospital beta blockers for TBI, as evidence has historically been limited to low quality, observational studies.[14] It is difficult to ascertain whether the administration of exogenous catecholamines through the systemic circulation replicates any of the effects of the previously described innate catecholamine surge, although a previous study in TBI patients has shown that those who received exogenous norepinephrine had both higher systemic and central levels of norepinephrine, suggesting that central levels may

Table 2
Comparison of VP+ and VP- patients with respect to additional diagnoses, procedures, and echocardiography results.

	Total (n = 556)	VP (+) (n = 83)	VP (−) (n = 473)	p value
Additional Diagnoses				
- Diabetes Insipidus, % (n)	0.4% (2)	2.4% (2)	0% (0)	0.02
- SIADH, % (n)	1.4% (8)	2.4% (2)	1.7% (8)	0.61
- Cerebral salt wasting, % (n)	0.5 (3)	3.6% (3)	0% (0)	<0.01
Procedures				
- Angioembolization, % (n)	1.4% (8)	3.6% (3)	1.1% (5)	0.10
- Craniectomy, % (n)	4.1 (23)	16.9% (14)	1.9% (9)	<0.01
- Craniotomy, % (n)	8.8% (49)	16.9% (14)	7.4% (35)	<0.01
- EVD, % (n)	4.5% (25)	10.8% (9)	3.4% (16)	<0.01
- ICP monitoring device placement, % (n)	4.3% (24)	21.7% (18)	1.3% (6)	<0.01
- Intubation, % (n)	24.6% (137)	78.3% (65)	15.2% (72)	<0.01
- Laparotomy, % (n)	2.3% (13)	12.0% (10)	0.6% (3)	<0.01
- Other				
- Maxillofacial, % (n)	2.0% (11)	2.4% (2)	1.9% (9)	0.67
- Orthopedic, % (n)	10.4% (58)	18.1% (15)	9.1% (43)	0.14
- Spine, % (n)	1.4% (8)	6.0% (5)	0.6% (3)	<0.01
Echocardiography results				
- Lowest EF, %	60.8 ± 13.2 64 (57–69)	58.1 ± 18.3 64 (47–73)	61.6 ± 11.4 64 (58.5–68)	0.30
- Wall motion abnormality, % (n)	17.5% (32/183)	31.3% (15/48)	12.6% (12/135)	<0.01
- Hyperdynamic changes, % (n)	18.0% (33/183)	25.0% (12/48)	15.6% (21/135)	<0.01

Continuous values are reported as means ± standard deviation (SD), median (interquartile ranges), unless otherwise specified.
EF, ejection fraction; EVD, external ventricular drain; ICP, intracranial pressure; SIADH, syndrome of inappropriate antidiuretic hormone secretion

Table 3
Comparison of VP+ and VP- patient outcomes.

	Total (n = 556)	VP (+) (n = 83)	VP (−) (n = 473)	Mean difference (95% CI)/Odds ratio (95% CI)	p value
Hospital LOS, d	10.0 ± 12.1 6 (3–12)	18.1 ± 17.9 13 (4–26)	8.6 ± 10.1 5 (3–10)	9.5 (5.5–13.5)	<0.01
ICU LOS, d	4.5 ± 5.4 2 (2–4)	10.6 ± 9.2 6 (3–16)	3.4 ± 3.4 2 (2–3)	7.2 (5.2–9.3)	<0.01
Ventilator days, d	6.2 ± 5.0 4 (2–10)	7.0 ± 5.9 4 (2.5–11)	5.5 ± 3.9 4 (2–8.5)	1.5 (−0.2–3.2)	0.09
Inpatient mortality, % (n)	9.2% (51)	42.2% (35)	3.4% (16)	20.8 (10.7–40.4)	<0.01

Continuous values are reported as means ± standard deviation (SD), median (interquartile ranges), unless otherwise specified.
CI, confidence interval; ICU, intensive care unit; LOS, length of stay.

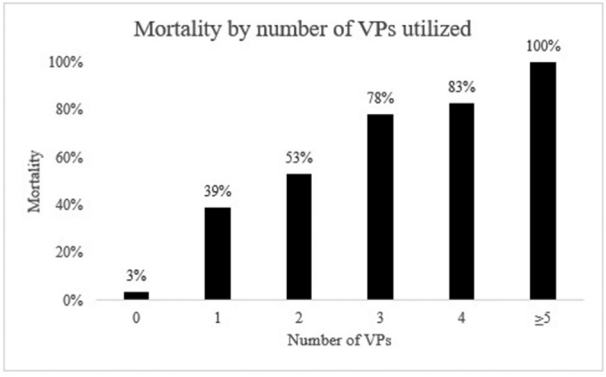

Fig. 2. Mortality by number of VPs utilized.

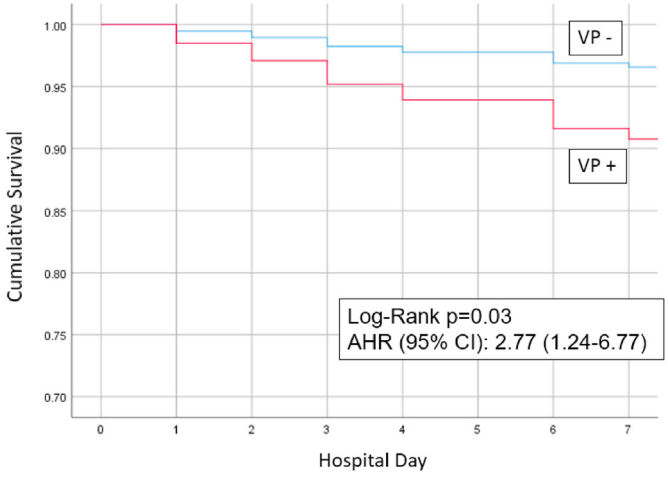

Fig. 3. Kaplan-Meier curve of survival with respect to VP use.
AHR, adjusted hazard ratio; CI, confidence interval; VP, vasopressor.

rise due to a disrupted blood brain barrier.[15]

Vasopressin may be used in addition to, or at times, in lieu, of catecholamines. Previous research has identified vasopressin as a key mediator in the human response to injury.[16,17] In fact, deficiency in vasopressin levels may lead to intractable shock.[18] A recent double-blinded randomized controlled trial showed that supplementation with low dose arginine vasopressin was associated with transfusion of decreased blood products.[19] Recent studies examining the role of vasopressin for brain injury specifically have been associated with varying outcomes with respect to cerebral perfusion.[20–22] Our data are unable to speak to the effect of

vasopressin in isolation, as all patients who received vasopressin were also given at least one additional VP.

The limitations of this study are related to its retrospective nature and the inability to decipher the indication for VP use. Thus we were not able to distinguish VP use for other indications such as hemodynamic support in the setting of sepsis or hypovolemia. These indications however, are unlikely given that the median interval from admission to the initiation of VP was 1 day. Intoxication status upon admission was not accounted for. Additional blood transfusions, interventions, or pharmacologic therapies were not accounted for. Patients with minor TBI were not excluded to allow for an ample sample size for further analysis. Given the study design, only association of mortality and not causation can be stated. Although we reviewed the echocardiogram reports for those who had it available, we could not account for fluid balance status, nor how ICP measurements influenced VP utilization. Despite these limitations, these results offer an insight on the use of VP in TBI patients admitted to the ICU and quantify their association with mortality.

Conclusions

Vasopressors are commonly used for patients with traumatic brain injury admitted to the intensive care unit. Patients who require vasopressors have a significantly higher injury burden. Although these agents may be useful for the temporary improvement of the cerebral perfusion pressure or in avoiding hypotension, their use is not associated with improved survival. Future research should focus on discriminating the effect of endogenous and exogenous catecholamine release on the physiology of severe traumatic brain injury patients and on exploring alternatives to avoid secondary insults to the brain and improve cerebral perfusion pressures.

References

1. Huijben JA, Volovici V, Cnossen MC, et al. Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Crit Care*. 2018;22(1):90.
2. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury. *Neurosurgery*. 2017;80(1):6–15. fourth ed.
3. Sookplung P, Siriussawakul A, Malakouti A, et al. Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. *Neurocritical Care*. 2011;15(1):46–54.
4. Fernandez-Ortega JF, Baguley IJ, Gates TA, Garcia-Caballero M, Quesada-Garcia JG, Prieto-Palomino MA. Catecholamines and paroxysmal sympathetic hyperactivity after traumatic brain injury. *J Neurotrauma*. 2017;34(1):109–114.
5. Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M. Catecholamines predict outcome in traumatic brain injury. *Ann Neurol*. 1987;21(5):438–443.
6. Johnston AJ, Steiner LA, Chatfield DA, et al. Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. *Intensive Care Med*. 2004;30(5):791–797.
7. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24:294–302.
8. McIntosh TK, Yu T, Gennarelli TA. Alterations in regional brain catecholamine concentrations after experimental brain injury in the rat. *J Neurochem*. 1994;63(4):1426–1433. https://doi.org/10.1046/j.1471-4159.1994.63041426.x.
9. Rizoli SB, Jaja BNR, Di Battista AP, et al. Catecholamines as outcome markers in isolated traumatic brain injury: the COMA-TBI study. *Crit Care*. 2017;21(1):37.
10. Lozano D, Gonzales-Portillo GS, Acosta S, et al. Neuroinflammatory responses to traumatic brain injury: etiology, clinical consequences, and therapeutic opportunities. *Neuropsychiatric Dis Treat*. 2015;11:97–106.
11. Salim A, Hadjizacharia P, Brown C, et al. Significance of troponin elevation after severe traumatic brain injury. *J Trauma*. 2008;64(1):46–52.
12. Kinoshita K. Traumatic brain injury: pathophysiology for neurocritical care. *J Intensive Care*. 2016;4:29.
13. Ley EJ, Leonard SD, Barmparas G, et al. Beta blockers in critically ill patients with traumatic brain injury: results from a multicenter, prospective, observational American Association for the Surgery of Trauma study. *J Trauma Acute Care Surg*. 2018;84(2):234–244.
14. Alali AS, Mukherjee K, McCredie VA, et al. Beta-blockers and traumatic brain injury: a systematic review, meta-analysis, and Eastern association for the Surgery of trauma guideline. *Ann Surg*. 2017;266(6):952–961.
15. Mautes AE, Müller M, Cortbus F, et al. Alterations of norepinephrine levels in plasma and CSF of patients after traumatic brain injury in relation to disruption of the blood-brain barrier. *Acta Neurochir*. 2001;143(1):51–57. ; discussion 57-58.
16. Feinstein AJ, Cohn SM, King DR, Sanui M, Proctor KG. Early vasopressin improves short-term survival after pulmonary contusion. *J Trauma*. 2005;59(4):876–882. ; discussion 882-883.
17. Rajani RR, Ball CG, Feliciano DV, Vercruysse GA. Vasopressin in hemorrhagic shock: review article. *Am Surg*. 2009;75(12):1207–1212.
18. Cohn SM, DeRosa M, McCarthy J, et al. Characterizing vasopressin and other vasoactive mediators released during resuscitation of trauma patients. *J Trauma Acute Care Surg*. 2013;75(4):620–628.
19. Sims CA, Holena D, Kim P, et al. Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial. *JAMA Surg*. 2019;154(11):994–1003.
20. Dickson JM, Wang X, St John AE, Lim EB, Stern SA, White NJ. Damage control resuscitation supplemented with vasopressin in a severe polytrauma model with traumatic brain injury and uncontrolled internal hemorrhage. *Mil Med*. 2018;183(9-10):e460–e466.
21. Allen CJ, Subhawong TK, Hanna MM, et al. Does vasopressin exacerbate cerebral edema in patients with severe traumatic brain injury? *Am Surg*. 2018;84(1):43–50.
22. Van Haren RM, Thorson CM, Ogilvie MP, et al. Vasopressin for cerebral perfusion pressure management in patients with severe traumatic brain injury: preliminary results of a randomized controlled trial. *J Trauma Acute Care Surg*. 2013;75(6):1024–1030. ; discussion 1030.