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Prospective Evaluation of Post-Traumatic Vasospasm and Post-Injury Functional Outcome Assessment: Is Cerebral Ischemia Going Unrecognized in Patients with Traumatic Brain Injury?

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Abstract

Background: Secondary injury processes such as posttraumatic vasospasm (PTV) play a critical role in the development of cerebral ischemia/infarction after traumatic brain injury (TBI). The objectives of this study were to evaluate the incidence of cerebral vasospasm in patients with moderate to severe TBI and to assess post-injury functional outcome. **Study Design:** A prospective observational study was conducted in patients with moderate and severe blunt TBI. Transcranial Doppler (TCD) ultrasound was performed within the first 72 hours and then daily for up to 7 days. Patient characteristics and outcome data including functional outcome as assessed by the Extended Glasgow Outcome Scale (GOS-E) were collected and compared between patients with and without PTV. **Results:** Twenty-three patients met our inclusion criteria. While there was a 47.8% incidence of vasospasm as detected by TCD, there was no significant difference in hospital LOS or mortality between patients with and without PTV. Of the two patients with PTV who died, both had a cerebral infarct or cerebral ischemia. In evaluating overall GOS-E among patients with a cerebral focal injury, patients with PTV had a significantly higher GOS-E score when compared to patients without PTV (8.0 vs. 6.8, $p = 0.01$). **Conclusions:** The high incidence of PTV and the role of clinically significant vasospasm after TBI remain unclear. While functional outcome was better in patients with a focal injury and vasospasm, patients who died had cerebral ischemia or infarction. We hypothesize that there is an interaction between impaired cerebral autoregulation, PTV and poor outcomes in patients with TBI.

Keywords

Traumatic Brain Injury, Vasospasm, Cerebral Ischemia

1. Background

Traumatic brain injury (TBI) affects 1.5 million Americans per year, resulting in over 50,000 deaths and 230,000 hospitalizations annually. While more than 750,000 sustain a short-term disability, approximately 90,000 suffer permanent impairment [1]. Secondary injury processes such as increased intracranial pressure (ICP), systemic arterial hypotension and hypoxia, and cerebral hypoperfusion play a critical role in the development of ischemia after trauma to the central nervous system and occur hours-to-days after the primary insult [2] [3]. Cerebral ischemia occurs when there is decreased blood flow and oxygen to the brain leading to cerebral hypoxia. When cerebral hypoxia progresses to cell and brain tissue death, cerebral infarction ensues. Ischemia has been described as the single most important secondary insult [4] and has been identified histologically in approximately 90% of patients who die following closed head injury [5].

Cerebral vasospasm can profoundly impact neurological recovery and functional outcome [6]. Vasospasm has been described as a sustained arterial narrowing and is classified as either angiographic or clinical [7]. Angiographic vasospasm refers to the visible narrowing of the dye column on cerebral angiogram. Clinical vasospasm is the functional manifestation of cerebral ischemia produced by this arterial narrowing (vasoconstriction) [8]. Clinically, the onset of new or worsening neurological symptoms is the most reliable indicator of cerebral vasospasm following a ruptured cerebral aneurysm. However, cerebral vasospasm may go unrecognized in patients suffering from moderate to severe TBI [9]. These patients frequently are altered from their primary brain injury, narcotic use for pain, and from the use of paralytics/sedatives while on mechanical ventilation for airway protection. These patients are also difficult to evaluate with respect to neurological symptomatology due to concomitant injuries. Thus, relying on the neurological exam to observe deteriorating neurological signs consistent with posttraumatic vasospasm (PTV) may not be feasible. As a result, PTV causing cerebral ischemia and posttraumatic cerebral infarction (PTCI) may be going unrecognized in the patient with TBI.

While the etiology and outcome of patients with vasospasm secondary to ruptured aneurysm is well described, the clinical significance of posttraumatic vasospasm is a topic of debate. The objective of this study was to evaluate the incidence of cerebral vasospasm in patients with moderate to severe TBI and to assess their functional outcome at 3 and 6 months post-injury.

2. Methods

A prospective, observational study was conducted in patients with moderate and

severe blunt TBI who were admitted to the R Adams Cowley Shock Trauma Center between October 2012 and December 2013. Moderate TBI was defined as a post-resuscitation (per standard Advanced Trauma Life Support [ATLS] resuscitation Guidelines) Glasgow Coma Scale (GCS) score 9 - 12 and severe TBI was defined as a post-resuscitation GCS score 3 - 8. Patients with a head Abbreviated Injury Scale (AIS) score > 2 and intracranial pressure (ICP) monitoring were included. Head AIS > 2 was defined as hemorrhage, focal injury (*i.e.* contusion), or diffuse axonal injury (DAI) on non-contrast head computed tomography (CT). Patients determined to be non-survivable, with penetrating injuries, in custody or prisoners, or active military were excluded. Informed consent was obtained from the patient's Legally Authorized Representative (LAR). The management of patients followed established TBI management guidelines [10]. Transcranial Doppler (TCD) ultrasound assessment, performed by a trained transcranial doppler technologist, was performed on average within the first 72 hours of admission and then daily for up to 7 days. Vasospasm was defined by the Lindegard Ratio, the ratio of flow velocity in the middle cerebral artery to the blood flow velocity in the ipsilateral, extracranial internal carotid artery. Mild vasospasm was defined by a blood flow velocity of 120 cm/sec - 149 cm/sec and a Lindegard Ratio of3 to 4. Moderate vasospasm was defined by a blood flow velocity of 150 cm/sec - 199 cm/sec and a Lindegard Ratio of 4 to 6. Severe vasospasm was defined by a blood flow velocity of >200 cm/sec and a Lindegard Ratio of greater than 6. Patients with vasospasm were not given special treatment, as guidelines for treatment of posttraumatic vasospasm do not exist. The Extended Glasgow Outcome Scale (GOS-E) was used to measure long-term functional outcome and was administered by an experienced trauma research coordinator to study subjects via telephone at 3 months and 6 months post injury. A GOS-E score of 1 to 4 was defined as unfavorable functional outcome and a score of 5 to 8 was defined as favorable functional outcome.

Patient characteristics, including age, gender, admission GCS, admission systolic blood pressure (SBP), head AIS, Injury Severity Score (ISS), type of brain injury, and outcomes including mortality, hospital length of stay (LOS), and GOS-E were compared between patients with and without PTV. Categorical variables were compared by Pearson's chi-square statistic or Fisher's exact test. Numerical variables were compared by the Student's t test or the Wilcoxon rank-sum test. A p-value < 0.05 was considered statistically significant. Descriptive statistics were summarized using frequencies, percentages, means, standard deviations, medians and interquartile ranges (IQR). Repeated measures regression models were estimated for analysis of Extended Glasgow Outcome Scale (GOS-E) at 3 and 6 months. Mean parameter estimates and corresponding 95% confidence intervals (CI) based on the Student's t distribution were computed. This study received approval from the Institutional Review Board of the University of Maryland School of Medicine.

3. Results

Twenty-three patients met our inclusion criteria and were enrolled. The majority of patients had a median head AIS score of 4 (IQR 4 - 5) and median GCS score of 7 (IQR 3 - 9) (Table 1). The overall incidence of vasospasm was 47.8%. Admission SBP was significantly lower in patients with vasospasm (125 +/− 26 vs. 147 +/− 26, $p = 0.02$) (Table 1). The median days from admission to TCD assessment was 2.4 (IQR 1.4 - 2.7). Peak incidence of vasospasm occurred on day 5 (Figure 1). Of the patients with vasospasm, all were male, 63.6% had subarachnoid hemorrhage, 45.4% had mild vasospasm, and 54.6% had moderate vasospasm. When comparing patients with vasospasm to patients without vasospasm, there was no significant difference in head AIS, GCS, ISS, or type of brain injury.

Table 1. Demographics of patient population.

	All Patients (N = 23)	Vasospasm (N = 11)	No Vasospasm (N = 12)	*P*-Value
Age (years), median	44	44	38	0.40
Male	87.0%	100.0%	75.0%	0.22
Adm SBP (mean +/− SD)	137 +/− 23	125 +/− 12	147 +/− 26	0.02
Admission GCS				
3 to 8	73.9%	73.0%	75.0%	1.00
9 to 12	26.1%	27.0%	25.0%	1.00
Head AIS				
3	13.0%	9.2%	16.7%	1.00
4	39.0%	45.4%	33.3%	1.00
5	48.0%	45.4%	50.0%	1.00
ISS, median	34	36	32	0.23
Type of Brain Injury				
SAH	73.9%	63.6%	83.3%	0.37
SDH	47.8%	27.3%	66.7%	0.10
EDH	21.7%	27.3%	16.7%	0.64
ICH	13.0%	18.2%	8.3%	0.59
Focal Injury	43.5%	27.3%	58.3%	0.21
DAI	8.7%	9.1%	8.3%	0.74
IVH	17.4%	27.3%	8.3%	0.32
LOS (days), median	18	19	14	0.46
Mortality	21.7%	18.2%	25.0%	1.00

SBP: systolic blood pressure; GCS: Glasgow Coma Scale Score; AIS: Abbreviated Injury Severity Score; ISS: Injury Severity Score; SAH: subarachnoid hemorrhage; SDH: subdural hematoma; EDH: epidural hematoma; ICH: intracerebral hemorrhage; DAI: diffuse axonal injury; IVH: intraventricular hemorrhage; LOS: length of stay.

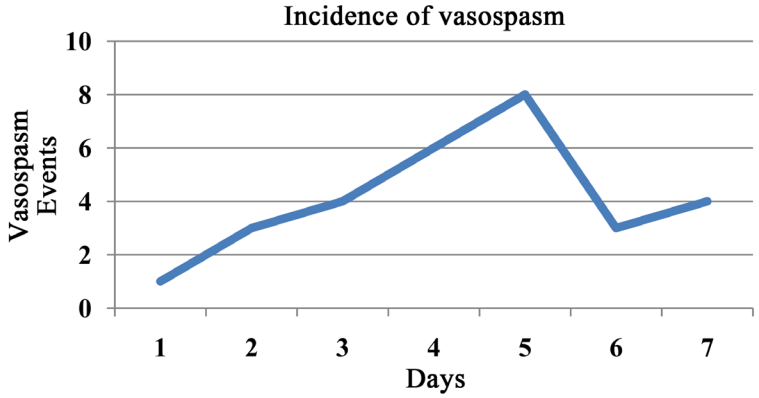

Figure 1. Daily incidence of vasospasm.

In evaluating outcomes in patients with or without vasospasm, there was no significant difference in hospital LOS and mortality, despite similar injury severity and type of brain injury. Of the two patients with vasospasm who died, both had evidence of cerebral ischemia and infarction.

In evaluating functional outcome, GOS-E score was evaluated in 17 patients at 3 months (Table 2). Of those 17 patients, 2 patients were lost to follow-up, resulting in 15 remaining patients who were evaluated at 6 months. When accounting for the correlation between measurements within a patient over time, there was no statistical significant difference in GOS-E scores at 6 months when compared to GOS-E scores at 3 months (5.8 vs. 5.2, $p = 0.07$). Similarly, in patients with and without vasospasm, there was no statistically significant difference in GOS-E scores at 6 months when compared to GOS-E scores at 3 months (5.8 vs. 5.2, $p = 0.48$). In addition, the effect of vasospasm did not differ from 3months to 6 months ($p = 0.17$) (Table 2).

Further analysis involved the adjustment of vasospasm by individual types of brain injury to determine if the effect of vasospasm on GOS-E might change. Of the types of brain injury, only focal injury was significant in the univariate analysis. Thus, when adjusted by focal injury as a possible confounding variable in a repeated measures regression model, both vasospasm and focal injury had significant effects on GOS-E (Table 2). There was a non-significant trend towards a higher GOS-E score in patients with vasospasm when compared to patients without vasospasm (6.5 vs. 5.1, $p = 0.05$). In addition, patients with focal injury had a significantly higher GOS-E score when compared with patients without focal injury (7.1 vs. 4.5, $p = 0.002$). Among patients with no cerebral focal injury, there was no significant difference in functional outcome for patients with versus patients without vasospasm (5.3 vs. 3.8, $p = 0.15$). However, in patients with a cerebral focal injury on their admission non-contrast head CT scan, the presence of vasospasm significantly affected their functional outcome. When compared to patients with a cerebral focal injury and no vasospasm, patients with a brain focal injury and vasospasm had a significantly higher GOS-E score (8.0 vs. 6.8, $p = 0.01$) (Table 3).

Table 2. Extended Glasgow Coma Outcome (GOS-E) scores.

	n	Mean	95% CI	*P*-Value
3 months	17	5.2	4.3 - 6.1	
6 months	15	5.8	4.8 - 6.8	0.07
Vasospasm				
No	17	5.2	3.9 - 6.5	
Yes	15	5.8	4.5 - 7.2	0.48
Vasospasm (adjusted by Focal Injury)				
No	17	5.1	4.2 - 6.0	
Yes	15	6.5	5.5 - 7.5	0.05
Focal Injury (adjusted by Vasospasm)				
No	20	4.5	3.6 - 5.4	
Yes	12	7.1	6.0 - 8.2	0.002

Table 3. Extended Glasgow Coma Outcome (GOS-E) in patients with and without Focal Injury

	Vasospasm			No Vasospasm			*p*
	n	Mean	95% CI	n	Mean	95% CI	
No Focal Injury	12	5.3	3.9 - 6.7	8	3.8	2.2 - 5.5	0.15
Focal Injury	3	8.0	7.4 - 8.6	9	6.8	6.5 - 7.1	0.01

4. Discussion

The current study sought to evaluate the incidence of cerebral vasospasm in patients with moderate to severe TBI and to assess functional outcome at 3 and 6 months post-injury. We found that PTV was detected in 48% of the sample population, which is similar to previously published reports [9] [11]. Despite the high incidence of PTV, there was no significant difference in mortality and hospital LOS between patients with and without PTV with similar injury severity and type of brain injury. However, of the patients with vasospasm who died, both had cerebral infarct or cerebral ischemia.

When assessing functional outcome, the GOS-E score for patients with vasospasm who had a cerebral focal injury on their admission non-contrast head CT scan, was significantly higher than for those without vasospasm. The finding of improved functional outcome in patients with cerebral vasospasm seems counterintuitive as vasospasm by definition results in sustained cerebral arterial vasoconstriction causing decreased cerebral blood flow (CBF) and delayed ischemic cerebral infarcts [12]. In fact, several previous studies support the hypothesis that posttraumatic vasospasm results in poor functional outcome. Lee [13] *et al.* prospectively evaluated 152 patients with blunt and penetrating TBI and assessed functional outcome at 6 months. He found that hemodynamically significant vasospasm was a significant predictor of poor functional outcome.

Ojaha [14] *et al*. evaluated 32 patients with blunt severe TBI and assessed GOS at 12 months. He found that the timing of vasospasm was related to functional outcome. When compared to patients with vasospasm occurring after 24 hours from injury, patients with early vasospasm (*i.e.* within the first 24 hours from trauma) had poor functional outcome at 12 months. Armondo [15] *et al.* retrospectively evaluated 57 patients with blast associated closed and penetrating TBI and found that patients with vasospasm had a lower GOS score at discharge compared to those without vasospasm. Finally, O'Brien [16] *et al*. prospectively evaluated 69 children with TBI. He found that among patients with moderate TBI, good neurologic outcome was found in 76% of patients without vasospasm and in 40% of those with vasospasm. In patients with severe TBI, good neurologic outcome was found in 29% of children without vasospasm and in 15% of those with vasospasm.

In our sample population, patients with vasospasm had a significantly lower admission SBP suggesting a direct relationship between vasospasm and low SBP. However, despite the lower admission SBP, there was no significant difference in outcomes and functional outcome at 3 and 6 months was improved. We hypothesize that the theory to explain the finding of improved functional outcome in patients with vasospasm involves cerebral autoregulation. Cerebral autoregulation is the intrinsic ability of the brain's vasculature to maintain adequate CBF independent of fluctuations in arterial blood flow. Normally, as regional cerebral perfusion pressure (rCPP) decreases, distal arterioles dilate. Vascular resistance is reduced, thus maintaining CBF and brain oxygenation. However, when vasodilation can no longer compensate for a reduction in rCPP, this autoregulatory mechanism fails resulting in the reduction of CBF. A decrease in CBF can result in cerebral ischemia and infarction. Impaired cerebral autoregulation occurs in some patients after TBI and is associated with poor outcome and increased mortality [17]. Hlatky [17] *et al*. evaluated 122 patients with severe TBI and found that 49% on Day 1 and 87% on Day 2 had impaired autoregulation. Panerai [18] *et al*. looked at the association between impaired cerebral autoregulation and outcomes of 32 patients with severe TBI and found that when comparing survivors versus non-survivors, impaired cerebral autoregulation is a predictor of poor outcome. A reduction in CBF secondary to impaired autoregulation increases the vulnerability of the brain to secondary brain ischemic insults and is a predictor of poor outcome [18]. We hypothesize that it is precisely this population where clinically significant vasospasm or vasospasm that results in ischemia and infarction occurs. The literature supports our hypothesis in patients with aneurysmal subarachnoid hemorrhage. Barth [19] prospectively evaluated 22 patients with non-traumatic subarachnoid hemorrhage (SAH) to determine whether there was a correlation between autoregulation, angiographic vasospasm, and functional outcome. He found that in patients with aneurysmal SAH, impaired autoregulation significantly correlated with vasospasm (p = 0.002) and poor functional outcome (p = 0.001).

In our study, we hypothesize that patients with vasospasm and cerebral focal injury who demonstrated improved functional outcomes likely had intact cerebral autoregulation and patients with poor outcome, including the two patients with cerebral ischemia and cerebral infarct who died had impaired cerebral autoregulation. This hypothesis supports the theory that patients with intact cerebral autoregulation are able to compensate for cerebral hypoxia secondary to vasospasm; whereas patients with loss of cerebral autoregulation are not able to compensate and are at risk for poor outcomes.

There are a number of limitations to our study. The small sample size of the study weakened the power of the study and is more characteristic of pilot data, limiting the conclusions that can be made. Additionally, the results are representative of a single institution's experience. TCDs are not dynamic measurements and can only capture vasospasm at moments in time rather than continuously; thus, episodes of vasospasm could have been missed within our patient population. In addition, the mean time to obtain a TCD measurement was day 2 to 3, post admission; thus, earlier episodes of vasospasm could have been missed. Six patients were lost to follow up at 3 months. Of the remaining 17 patients, 2 additional patients were lost to follow up at 6 months; therefore functional outcome data at 3 and at 6 months was not obtained in these patients. The extent of focal injury was not evaluated and thus a limitation. The type 2 error that occurred from the small sample size limits our ability to draw conclusions with respect to length of stay, mortality, and functional outcomes in patients with and without vasospasm.

Despite these limitations, we have demonstrated a high incidence of PTV but the clinical significance of vasospasm after TBI remain unclear. We actually found better functional outcome in patients with PTV; however, there was a subset in which PTV is likely to be highly clinically significant. We hypothesize that cerebral ischemia and infarction are likely going unrecognized in patients with moderate to severe TBI who have impaired cerebral autoregulation. Perhaps continuous monitoring of both cerebral autoregulation and PTV could potentially decrease secondary brain injury by the early identification of cerebral hypoxia. Brady [20] *et al*. validated the use of near infrared spectroscopy (NIRS) for continuously monitoring cerebral autoregulation in cardiac surgery patients undergoing cardiopulmonary bypass. In this same patient population, Ono [21] *et al*. later found that not only was autoregulation was impaired, but a significant correlation between cerebral autoregulatory values in NIRS and mean velocity indices of TCDs. In fact, Weigl's [22] 2016 meta-analysis on the application of optical methods in the monitoring of TBI supports the use of NIRS for the assessment of cerebral autoregulation and described the use of targeted individual autoregulation guided treatment of patients with TBI at the bedside.

Unlike the 2012 American Heart Association/American Stroke Association guidelines [23] for patients with aneurysmal SAH, there are no guidelines for the management and treatment of patients with traumatic SAH who develop vasospasm. In fact, unlike in other patient populations, we are not even monitoring

for vasospasm or cerebral autoregulation in patients with TBI. Further multcenter prospective trials examining the clinical significance of PTV and the role of impaired cerebral autoregulation in patients with moderate to severe traumatic brain injury, are warranted. By continuously monitoring cerebral autoregulation and posttraumatic cerebral vasospasm with methods such as NIRS, we have the potential to decrease secondary brain injury by the early identification of cerebral hypoxia before it develops into cerebral ischemia and even worse cerebral infarction.

Conflict of Interest

The authors have no conflict of interest to report and have received no financial or material support related to this manuscript.

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