Assessing Middle Cerebral Artery Blood Flow Velocities and Outcomes in Pediatric Severe Traumatic Brain Injury using Transcranial Doppler Ultrasound

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Abstract

Objective: To assess the impact cerebrovascular flow velocities of pediatric traumatic brain injury (TBI) patients using transcranial doppler (TCD) and to assess for acute and long-term clinical correlations.

Methods: This is a retrospective study of pediatric patients who suffered a severe TBI defined as Glasgow Coma Scale ≤ 8. A total of 47 patients were treated between January 2014 and August 2018 and all patients received TCD assessments for cerebral blood flow velocity for a total of 210 measurements. The primary outcome measure was the correlation between middle cerebral artery (MCA) mean flow velocities (MFVs) and clinical characteristics. MCA velocities were identified as high flow or low flow states using age-adjusted standardized velocities. Persistent low flow states were defined as >50% of TCD recordings per patient displaying the specified flow state without resolution to a flow state within 2 standard deviations of age-sex defined normal. Secondary outcomes included mortality and the global function using Pediatric Glasgow Outcome Scale-Extended (GOS-E Peds) at 3, 6 and 12 month and the association of the TCD findings to other physiologic variables at the time of scanning.

Results: Of the 47 patients, the mean age was 8.24 years (± 5.82) and there were 33 (70%) males and 24 (51%) Hispanic. At least 1 low flow velocity (≥2 SDs below age-normalized mean) was identified in 20 (43%) patients and at least one high flow (≥2 SDs above age-normalized mean) in 10 (21%) patients. There were no associations between demographics and single episodes of low or high flow velocity, however, patients aged >5 and ≤10 and non-Hispanic patients were more likely to have persistent low flow states. Persistent low flow states were significantly associated with mortality (p=0.014).

Conclusions: TCD can be used to assess cerebrovascular function following pediatric TBI and may be used to for earlier identification of abnormal flow velocities.

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in children, with over 475,000 children annually visiting emergency departments in the United States, 35,000 hospitalizations, and 26,000 deaths (1). The primary injury can be eliminated or mitigated with injury prevention. However following injury, the goals of clinical management are to minimize the number and extent of second insults and lessen the secondary injury that may contribute to further tissue loss or damage (2). This has been thought to occur primarily through alterations in cerebral perfusion due to changes in cerebral blood flow (CBF) and cerebrovascular reactivity with potential correlation to clinical outcome (3). Cerebrovascular reactivity is the response of the cerebral blood vessels to a vasoactive stimulus, primarily alterations in $PaCO_2$. Neurovascular events such as cerebral vasospasm (CVS) are thought to reduce CBF below critical thresholds leading to cerebral ischemia and have been seen in adult patients with aneurysmal (aSAH) and traumatic subarachnoid hemorrhage (4-6). Low flow states are gaining attention as a potential neurovascular complication with acute and chronic implications (7-9). The ability to measure this post-traumatic event has the potential for early identification of ischemia and hemodynamic perturbations in this age population but remains relatively under studied.

Transcranial doppler (TCD) ultrasound is a non- invasive, bedside point-of-care tool that may potentially be utilized to identify changes in cerebrovascular dynamics. Specifically, the identification of mean flow velocity through major cerebral vessels may serve as an indirect measure to assess changes in CBF (10). While TCD measures and

criteria for CVS have been validated in adults (11-16), few studies have investigated the clinical use of TCD in children with TBI (17-19). Despite this, a recent survey has shown that several existing pediatric neurocritical care centers use TCD during clinical care, often to determine timing of neuroimaging, how to manipulate cerebral perfusion pressure (CPP), and whether to perform surgical interventions (20). The combination of high utilization of TCD in pediatric neurocritical care in conjunction with a lack of standardized data presents a need for expanding understanding of the implications of various cerebral flow velocities, especially in the setting of acute cerebral injury such as TBI.

We sought to assess the cerebrovascular flow velocities of pediatric TBI patients using TCD and to assess for acute and long-term clinical correlations. Specifically, in this patient population, we aimed to characterize the relationships between clinical characteristics, TCD velocities and functional outcome using the GOS-E Peds score.

Methods:

This is a retrospective study of pediatric severe TBI patients, defined as Glasgow Coma Scale ≤ 8, at Phoenix Children's Hospital identified between January 2014 and August 2018. Patients received daily TCD examinations as part of institutional standard of care with insonation of bilateral MCA, extracranial internal carotid artery, and basilar artery territories. The technique for TCD has been well described (10-12, 21) but in summary, bilateral MCA and bilateral extracranial internal carotid arteries were insonated at 1-mm intervals and highest mean flow velocities were identified for purposes of this study. TCD studies were performed using a 2 M-Hz pulsed probe with a TCD machine (Sonora-Tek, Natus Neuro, Middleton, WI, USA; Spencer Technologies, Spentech, Inc.).

Other standard physiologic variables that were collected included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, mean arterial pressure (MAP), intracranial pressure (ICP), and CPP at time of TCD scanning. The primary outcome measure was the correlation between MCA mean flow velocities (MFVs) and 3-month Pediatric Glasgow Outcome Scale-Extended (GOS-E Peds) score. Identification of flow states was done through use of age and sex standardized flow velocities (22,23). MCA flow state was categorized as: normal (within 2 standard deviation), low flow ($\geq$ 2 standard deviations below normal) and high flow ($\geq$ 2 standard deviations above normal). Persistent low or high flow velocities were defined as >50% of TCD recordings per patient displaying the specified flow state without resolution to a flow within 2 standard deviations of age-sex defined normal. Additionally, when assessing high flow states, Lindegaard ratios were calculated as the ratio of the mean velocity in the MCA compared to the ipsilateral ICA in order to distinguish between hyperemia and cerebral vasospasm as defined in the adult literature by a LR value less than 3 and greater than or equal to 3, respectively (3, 12, 7, 17). Secondary outcomes included the GOS-E Peds 6 and 12 months and the association of the TCD findings to other demographic and physiologic variables. A favorable outcome by GOS-E Peds was defined as $\leq$4, whereas a poor outcome was > 4, consistent with previous reported literature (7, 24). This study was reviewed and approved by Phoenix Children's hospital Institutional Review Board (IRB#17-142)

Statistical Analysis

Descriptive statistics were used to summarize the dataset and compare observed flow velocities to standardized normal velocities. Deviations from normal were measured in units of standard deviation from age-adjusted normal values. Physiologic measures, demographic and clinical characteristics were summarized using means with standard deviation or median with interquartile range as appropriate. Bivariable analyses including chi-square, Fisher's exact test, t-test, Mann-Whitney U, and Wilcoxon signed rank tests were used to assess associations between clinical characteristics and MCA MFVs, and similarly to assess if the presence of these perturbations were associated with clinical or physiologic changes. Associations with GOS-E Peds at 3, 6, and 12 months were assessed using chi-square and Fisher's exact test as appropriate test. All statistical analyses were performed in SAS, version 9.4 (SAS Institute Inc).

Results:

Of the 47 patients identified, there were 33 (70%) males, 24 (51%) Hispanic patients, with a mean age was 8.24 years (± 5.82). The most common mechanism of injury was motor vehicle related collision (51%) and most injuries were closed TBIs (89%). There were 3 deaths (6.4%), occurring in the acute setting secondary to their injuries. The mean GOS-E Peds scores at 3, 6, and 12 months were 4.3 (± 1.99), 4.2 (± 1.97), and 3.6 (± 2.07) respectively. For the 47 patients, there were 210 individual TCD recordings, (average 4.5 recordings per patient).

There were 20 (43%) patients who recorded at least 1 low flow velocity (≥ 2SDs outside normalized values), 10 (21%) patients were recorded to have at least 1 high flow velocity (≥ 2 SDs outside normalized values with accompanied LR ≥ 3), and 1 (2%) patient who recorded both a high and a low flow velocity. Patient age proved to be the only demographic factor independently statistically associated with flow velocity (Table 1). We found no differences in GOS-E Peds scores based on single incidences of low and high flow velocity but did note all 3 deaths occurred in patients with ≥ 1 low flow velocity. Significant associations were found occurred when assessing variables associated with persistently low flow velocities including age, death, and race (Table 2). There were no significant associations with persistent high flow states.

Examination of individual TCD episodes revealed 46 discrete incidences of low flow velocity and 69 instances of high flow velocity (Figure 1). Of the 69 episodes of elevated MCA velocity, 36 (52%) had an accompanying LR greater than 3 (Table 3). Additionally, there were significant associations with decreased hemoglobin (mean 10.35 g/dL in normal flow state compared to 9.6 g/dL in high flow state). Flow states were not otherwise associated with concurrent measures such as PaO2, PaCO2, HR, SBP, ICP or temperature. Additional assessment of the trends for patients with low flow states found that following detection of low flow velocity 8 (40%) patients later recovered to normal flow velocities. Following detection of high flow velocity 4 (40%) patients later recovered to a normal flow velocities.

Discussion:

Few studies have investigated the clinical correlations between TCD velocities and clinical outcomes in children following TBI. We identified 20 patients (43%) with at least one low flow state and 10 (21%) with at least 1 high velocity flow state. These results are the first reported for a majority Hispanic pediatric population. The incidence of low flows was significantly higher than previous reports of 6%, while the incidence of high flow velocities were within range of previous reports (7, 25, 26). The increase in low flows in our population could be due to intracranial hypertension or other local metabolic derangements. The only significant association occurred between age and patients with one single episode of abnormal flow velocities, particularly that children aged 5-11 showed lower flow velocities even when using age-normalized values. This is likely a reflection of severity of injury rather than intrinsic susceptibility of children in those ages. We sought to better assess the possible relationships between low flow states and demographics by assessing the subgroup of patients who had persistent low flow velocities. Using this method, we noted novel differences in velocities by race with Hispanic patient less likely to have persistent low flow velocities. While the sample size is relatively low, this is the first observation of this particular racial difference in this population. One possible mechanism for such a finding are differences in genetic influences on neuroplasticity such as APOE polymorphisms (27, 28). Another particularly noteworthy significant finding is that all 3 patients who died in the study sustained persistent low flow velocities. This adds to expanding literature into the correlation with death and low flow (7). Whether low flow leads to higher likelihood of

mortality or more severe injury leads to cerebrovascular pertubations remains unclear and requires further study.

This study also sought to further examine underlying physiology of patients with abnormal flow velocities. Specifically, our population demonstrated significant differences in hemoglobin levels at time of TCD assessment with high flow states being associated with low hemoglobin levels. Previous studies have shown that anemic states, defined as hemoglobin <10g/dL, are associated with poor outcomes in aSAH (29-31). While the difference in hemoglobin levels (10.35 g/dL vs 9.6 g/dL) could be argued to be clinically insignificant, the correlation could suggest a need to correct for these levels in the future or that smaller changes in blood viscosity may affect cerebral flow dynamics. Unlike previous studies, we found no significant relationship between temperature and high flow state (32). However, the collected temperatures were recorded after admission to the ICU for monitoring and may not be reflective of the original physiologic response. Additionally, despite the worse clinical course for patients with low flow states, these measurements were not associated with systemic hypotension, ICP, or derations in systemic CO_2. This may indicate other unmeasured alterations in CBF that are not mediated by blood pressure including impaired autoregulation or impaired CO2 reactivity (33,34). This may warrant further investigation into the cerebrovascular physiology of vasospasm in pediatric TBI patients with implementation of anatomical neuroimaging studies.

There were limitations to this study. The first is the small sample size which likely hindered the study's ability to capture the long-term impacts of single flow recordings. To further examine the role of race, a larger sample of patients and

longitudinal prospective data is required. Also, due to the retrospective nature of the study, the TCD examinations were not performed following a time standardized protocol, but rather as a daily screen for changes in velocity and potential for CVS as a potential contributor of ischemia. Similarly, this study was hindered by lack of consistency of TCD machines utilized, frequency of measurements, and frequency of full vessel insonation. Additionally, we did not consistently obtain anatomical neuroimaging to confirm TCD values suggestive or concerning for CVS, so our ability to infer the significance of such findings is limited.

Conclusions:

This study adds to expanding literature describing the diverse cerebrovascular dynamics of pediatric TBI patients with unique findings related to low flow velocities and implications of patient race. Further studies are needed to evaluate the complex cerebrovascular physiology of pediatric TBI assessed by TCD and correlate findings with other measures of cerebral autoregulation and anatomical neuroimaging.

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Figure 1:

Distribution of TCD detected flow velocities measured as standard deviations from normalized values.