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Day-to-Day Change in Pulsatility Index Describes Anterior Cerebral Circulation Disturbance and Functional Outcomes in Pediatric Traumatic Brain Injury

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Abstract

BACKGROUND: Traumatic Brain Injury (TBI) is a significant source of morbidity and mortality in children. Transcranial Doppler (TCD) ultrasound measures the cerebral arterial circulation allowing for the calculation of pulsatility indices (PI) that provide an assessment of cerebral blood flow alterations. However, the use of PI in children with TBI is poorly understood and may be an important measure for the nursing care of children.

OBJECTIVES: The purpose of this article is to define day-to-day PI change and to describe its relationship to injury characteristics and functional outcomes in children with TBI.

METHOD: We performed a secondary analysis of a prospective observational parent study of forty children aged 2 months to 15 years of age with mild, or moderate-severe TBI who had serial TCDs. Sequential TCD PI measurements of day-to-day change revealed several consistencies among the TBI severity groups.

RESULTS: Day-to-day PI change was higher in children with moderate-severe injury (40%) when compared to mild injury (21%). Greater day-to-day PI change was seen in children whose Glasgow Outcome Scale-Extended Pediatrics (GOS-E Peds) scores worsened (25%) compared to those who had an improved (19%) or unchanged GOS-E Peds scores (23%).

DISCUSSION: This study is the first to report day-to-day PI change in children with TBI and provides early insights into anterior cerebral artery circulation alterations of children with TBI. Although further nursing research is needed, this study provides early evidence that TCD may be a valuable non-invasive neuromonitoring option in the management of children with TBI.

In the United States, over 2.8 million individuals sustain a traumatic brain injury (TBI) annually.¹ One-third of all injury-related deaths in children under the age of 19 years old is

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the result of TBI, totaling over 7,400 children annually.² Children who survive TBI are at higher risk for developmental delay, mental health disorders, physical disabilities, and neurologic impairment when compared to the general pediatric population.^{3,4} The economic burden of pediatric TBI is significant at an average lifetime cost of \$600,000 to \$1,875,000.⁵

TBI occurs when there is an injury to the brain by either direct or indirect external mechanical force, which results in two injury phases.⁶ The primary injury phase occurs at the moment of injury impact and is the result of mechanical forces that structurally disrupt and/or damage the brain, including axonal tearing, hemorrhage, compression, and contusions.⁷ Secondary injury, occurring over minutes to days following the primary injury, results in hypoxia, altered cerebral blood flow, metabolic dysregulation and neuroinflammation.⁷ Therefore, assessment of injury in the secondary injury phase is critical to promote optimal neuroprotection that can lead to improved outcomes. Nurses, as bedside clinicians, may be more sensitive to changes within the patient that may be masked by lack of invasive neuromonitoring, such as increasing intracranial pressure. Noninvasive bedside-based neuromonitoring options to detect potential ongoing secondary brain injury remain limited in children with TBI.

Transcranial Doppler ultrasonography (TCD) is a non-invasive, portable, safe, and inexpensive imaging modality, that allows clinicians to measure cerebral circulation.^{8,9} While TCD remains an emerging area of research in pediatric TBI, TCD has been used to evaluate the anterior cerebral circulation via the middle cerebral artery (MCA).¹⁰ Evaluation of cerebral blood flow velocity (CBFV) in the MCAs can aid in the diagnosis of hyperemia and cerebral vasospasm.¹⁰ In preliminary studies, alterations in CBFV from baseline are associated with poorer neurologic outcomes in children with TBI.¹⁰ The use of TCD to measure CBFV includes the Gosling pulsatility index (PI). More commonly referred to as simply PI, the pulsatility index is a hemodynamic index that is calculated as the difference between systolic and diastolic flow velocities divided by the mean velocity $[(CBFV_{sys} - CBFV_{dia})/FV]$.¹¹ Alterations in PI have been associated with changes in intracranial pressure (ICP) and intracranial pathology.¹²⁻¹⁴ Recent case studies have demonstrated the potential for use of the TCD in the clinical management of pediatric patients with intracranial pathology.¹⁵ Therefore, the use of noninvasive bedside capable neuromonitoring such as a TCD allows the clinician to determine PI of the cerebral circulation, which provides insights into the physiological state of the brain after TBI.^{12,16,17} This technology being readily available at the bedside may improve nursing care and nurses' evaluation of applied therapies to treat ongoing secondary injury.

In existing research, PI is typically analyzed as a single measurement in time that may or may not be repeated. Day-to-day change is a novel concept that describes the change in the maximum PI measurement from one day to the next day. This concept is operationalized by calculating the percent change of the maximum PI measurement from one day to the subsequent day $[(PI_{day2} - PI_{day1}) / PI_{day1}]$. As a measure of cerebral vasculature dynamics, change in the PI measurements could theoretically provide insight into the cerebrovascular hemodynamics of an evolving TBI. The purpose of this study was to describe the day-to-day change of PI of the anterior circulation in children with TBI in the context of injury severity, sidedness of injury, change in outcome, and mortality.

Method

Parent and Daughter Studies

Following institutional review board approval and upon parental consent, the *parent study* recruited 60 children (age 10 days to 15 years) who were admitted to a tertiary-care level-1 trauma center hospital for a TBI from December 2012 through August 2015. The prospective exploratory study measured daily CBFV and PIs using TCD, cognitive and functional outcomes at time of discharge and first post-discharge follow-up visit. All participants were previously healthy with no known prior history of TBI and were enrolled into the study within 24 hours of admission. Enrollment criteria included: 1) English or Spanish speaking, 2) age of 5 days to 15 years, 3) ability to undergo adequate transcranial TCD, 4) diagnosis of TBI, and 5) admission to hospital. Children were excluded from participating if there was a previously diagnosed significant neurodevelopmental delay because a prior baseline neurocognitive function was unavailable to establish a comparison.

In this study, after institutional review board approval, a de-identified database of the recruited 60 children was screened for consecutive MCA PI measurements. This resulted in 42 children, aged 2 months to 15 years. Injury severity based on the Glasgow Coma Scale (GCS) for infants and children was determined at time of emergency department evaluation.¹⁸ All TBI severities (mild, moderate, severe) were included. We used the Glasgow Outcomes Scale Extended – Pediatrics (GOS-E Peds), a reliable and validated pediatric TBI specific measure of functional and cognitive outcomes at the time of discharge (T1) and 1-month post-discharge (T2).¹⁹ It uses an eight point scale with a score one (1) indicating upper good recovery through eight (8) indicating death.¹⁹ A decrease in GOS-E Peds score indicates an improvement in functional and cognitive outcome, while an increase indicates worsening functional and cognitive outcomes.

Participants in the parent study underwent an initial TCD by a sonographer trained in TCD within 24 hours of enrollment to the study and daily TCD examinations, which continued through hospital day 8 or discharge/death. The study protocol followed the method described by Aaslid and colleagues where the anterior circulation was measured by insonating the bilateral MCAs every 2–5mm at standard depths.⁸ A neurologist certified in TCD interpretation performed a blinded review of all TCD reports and determined the TCD interpretations.

Analysis

Data on the 43 children was downloaded from REDCap and IBM SPSS Statistics version 25 was used for this analysis. Descriptive statistics were used to describe the sample characteristics, day-to-day PI change (described below), and outcome measurements.

Children were grouped as either mild (GCS 13–15) or moderate-severe (GCS 3–12). All children were included in the initial analysis. However, we identified one child who only had unilateral measurements who was subsequently excluded. Additionally, we identified two children with extreme day-to-day PI change values of 294% & 77%. We then performed a second analysis excluding these two outliers to examine whether their values skewed day-to-

day change. Our final analysis therefore included a total sample of 40 children (SDC, Figure 1).

Measures for day-to-day change in PI was calculated as: 1) the highest daily PI highest daily PI on sequential days was used in the calculation, 2) day-to-day PI changes were calculated for the right middle cerebral artery (RMCA) and left middle cerebral artery (LMCA), 3) to determine the day-to-day change value, the following formula was used: $[(PI_{day2} - PI_{day1}) / PI_{day1}] = \text{day-to-day change}$, 4) the day-to-day change was multiplied by 100 to obtain the percent change then converted into an absolute value using the formula: $|\text{Day-to-day change} \times 100| = \text{day-to-day PI change}$. Day-to-day change was determined by calculating the average of the day-to-day PI change for each child.

This was calculated for the RMCA and LMCA individually as well as for the largest of either the RMCA or LMCA. The day-to-day change was evaluated in the context of severity, sidedness of injury, change in outcome, and mortality. The largest day-to-day change of either the RMCA or LMCA was evaluated in children with mild injury and compared to those with moderate-severe injury. We also explored whether sex as a characteristic demonstrated differences in PI day-to-day change. The day-to-day change in both the RMCA and LMCA in children with left, right, and bilateral injuries was examined. The day-to-day change was also evaluated based on change in GOS-E-Peds score between discharge and follow-up. Finally, children who died were compared to those who survived.

Results

In the initial analysis (n=43), the day-to-day PI change of the children with mild injury was 23.3% and 52.9% in children with moderate-severe injury. Whereas in the second and final analysis, which excluded the two outliers and child with only unilateral measurements (n=40), we found that children with mild injury had an average day-to-day PI change of 21%; and 40% in children with moderate-severe injury. The most represented in our sample of 40 children were mild TBI (60%), Caucasian (60%) and male (52.5%). Children with mild injury were hemodynamically stable whereas the moderate-severe TBI were managed based on the 2nd edition of the pediatric TBI management guidelines to maintain stable hemodynamics, optimal CPP, and optimal ICP.²⁰ Of the sample, only nine patients had ICP monitoring thereby limiting the opportunity to compare ICP to PI measurements. A majority of the children were diagnosed with a unilateral injury (65%). Table 1 provides additional characteristics regarding the study sample. In our sample, all children with moderate-severe injuries had higher day-to-day change of both the RMCA and LMCA PI (40%) compared to those with mild injury (21%). This remained true when evaluating for differences between sexes. When evaluating injury sidedness, children with right sided injury had a greater day-to-day change of PI in the LMCA (26%) when compared to the RMCA (18%). Children with left sided injury had the largest day-to-day change of PI in the LMCA (23%) compared to the RMCA (20%). Children with bilateral injury have comparable day-to-day change of the RMCA (27%) and the LMCA (26%) (Figure 1). A difference in day-to-day PI change was seen in both mild injury and moderate-severe injury groups. In mild injury, a larger day-to-day PI change was seen in children whose GOS-E Peds worsened (25%) between discharge and follow up compared to those with no change (23%) or improved GOS-E Peds

score (19%). Similarly, in moderate-severe injury, a larger day-to-day PI change was seen in children whose GOS-E Peds did not change (42%) compared to those whose improved (37%). No children in the moderate-severe group had worsening GOS-E Peds scores (SDC, Figure 2). Children who died during their hospitalization had higher day-to-day PI change (60%) when compared to those who survived (27%).

Discussion

This study provides initial insights into this concept and describes the day-to-day change in MCA PI in children with TBI. This early evidence suggests that the use of TCD to measure day-to-day PI change in children with either mild or moderate-severe TBI may be helpful in monitoring the cerebral vasculature in the secondary injury phase.

Our study demonstrated that day-to-day change of the PI in the anterior circulation differed based on TBI severity. The children with moderate-severe TBI had consistently higher day-to-day PI change when compared to those with a mild injury, which was likely a result of a more hyperdynamic cerebral circulation. Day-to-day PI changes may provide an opportunity to capture the compensatory mechanism in response to a severe injury or cerebrovascular dynamics due to the injury. A PI change reflecting a compensatory distal vasodilation related to hypoperfusion has been seen in patients with large-vessel vasospasm after subarachnoid hemorrhage.²¹

Previous research has produced conflicting results of the interpretation of PI in the setting of intracranial pathology. A positive correlation between PI and ICP in both children and adults with severe TBI has been noted.²² Additionally, a strong positive correlation between ICP and PI in both children and adults with various types of intracranial pathologies was seen.¹² This change of results may be explained by PI being not specifically a measure of cerebrovascular resistance but rather a complex relationship between CPP, arterial pressure, heart rate, and compliance of the cerebral arterial bed.²³ In our study, children with mild injury, who had stable vital signs and hemodynamics had lower day-to-day PI change, which suggests they had an intact cerebrovascular response to the injury and supports these previous findings.²³

When sidedness in day-to-day change was compared to side of injury, the analysis revealed a consistent pattern. Higher day-to-day PI change was seen in the LMCA in children with right sided injury. Although suggestive of a cerebrovascular compensatory mechanism we also found higher day-to-day PI change in the LMCA in children with left sided injury. The same side finding may be the result of a small sample size because only nine children demonstrated these findings. However, in children with right sided injury the difference in the day-to-day PI change of the LMCA was larger (26%) compared to the RMCA (18%) increasing the likelihood of a consistently higher day-to-day change of the contralateral MCA if evaluated in a larger sample.

In addition to injury severity and cerebrovascular dynamic insight, day-to-day PI change may have prognostic value by providing insight into ongoing injury and need for either further hospital observation in the mild TBI patient. Nurses are well positioned to advocate

for the use of this technology to promote more timely insight into the cerebral circulation and respond to therapeutic modalities. Previous research supports the risk of worse neurological outcome with increased PIs. In adolescents and adults with mild-moderate TBI and an abnormal PI (≥ 1.25) or FVd (≤ 25) on admission predicted neurological decline within seven days.²⁴ This is consistent with our results that demonstrated that regardless of PI value, patients who had a stable PI tended to have better outcomes than those with highly variable PI. Using the GOS-E Peds as a measure of global outcome, day-to-day PI change was increased in those whose GOS-E Peds scores either did not change or worsened between discharge and 1 month follow up. These early findings suggest that measuring daily PIs and assessing for day-to-day change may provide data that clinicians could use to counsel patients and families on likelihood of continued neurologic improvement or decline. However, in children at risk for death as a result of their brain injury, day-to-day PI change was less helpful. Although in our study children who died had a higher day-to-day PI change when compared to those with moderate-severe injury who survived, the change in the group average day-to-day PI change by removing the deceased children was only 3%. This demonstrates that day-to-day PI change was less sensitive in the children whose cerebral circulation was increasingly more impaired and who required more hemodynamic support to provide optimal CPP.²³

Limitations

In this study, the smaller convenient sample excluded children who did not have documented serial bilateral PI measurements thereby only providing early trending evidence. By examining an absolute value of day-to-day PI change directionality could not be declared. In future studies, evaluating for directionality may provide further insights into PI as a neuromonitoring measure. Additionally, we were unable to evaluate PI as a surrogate for ICP due several limitations.

Conclusion

Day-to-day PI change as measured by TCD may provide insight into the anterior cerebral circulation after TBI thereby providing clinicians with additional information to assess the secondary injury phase and potential cerebral circulation disturbances. Future nursing research with statistical analysis could provide further explanation as to the relationship between day-to-day PI change and cerebral circulatory disturbances in the secondary injury phase. Additionally, this work demonstrates TCD's role in the management of children with TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Mean Day-to-Day Variability of the MCA PI by subject characteristic
Legend: MCA, middle cerebral artery; PI, pulsatility index

Table 1.**Individual Characteristics and Demographics**

Characteristic	Sample n=40	(%)
Sex		
Female	19	(47.5%)
Male	21	(52.5%)
Race/Ethnicity		
American Indian or Alaskan Native	1	(2.5%)
Asian	1	(2.5%)
Black / African American	13	(32.5%)
Other	1	(2.5%)
White / Caucasian	24	(60%)
Age		
Less than 6 months	9	(22.5%)
6 months to 3 years	6	(7.5%)
4 years to 6 years	5	(12.5%)
7 – 15 years	18	(45%)
Severity of Injury		
Mild	24	(60%)
Moderate-Severe	16	(40%)
Sidedness of Injury		
Right Side	17	(42.5%)
Left Side	9	(22.5%)
Bilateral	14	(35%)
GOS-E Peds at Time 1		
Upper Good	8	(20%)
Lower Good	13	(32.5%)
Upper Moderate	5	(12.5%)
Lower Moderate	3	(7.5%)
Upper Severe	3	(7.5%)
Lower Severe	6	(15%)
Dead	2	(5%)
Missing	0	(0%)
GOS-E Peds at Time 2		
Upper Good	11	(27.5%)
Lower Good	11	(27.5%)
Upper Moderate	5	(12.5%)
Lower Moderate	1	(2.5%)
Upper Severe	2	(5%)
Lower Severe	4	(10%)
Dead	2	(5%)
Missing	4	(10%)

GOS-E Peds, Glasgow Outcome Scale-Extended Pediatrics

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