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Age-specific cerebral perfusion pressure thresholds

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Anonymous party-goer “What do you do?”

Thomas V. Brogan, MD “I deliver oxygen.”

The neurocritical care of children and adults with acute traumatic brain injury (TBI) is largely designed to minimize secondary injury, and the most important component of this approach is to prevent or limit global or regional cerebral ischemia.(1-3) The relationship between cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) in the injured child’s brain is known to be complex.(4) However, in the setting of impaired autoregulation, CPP may be more directly related to CBF and thereby cerebral oxygen and substrate delivery. Unlike CBF, CPP can be easily and continuously calculated in patients with intracranial pressure (ICP) and invasive arterial blood pressure (BP) monitors. Providers at the bedside can then adjust therapies in real time with CPP-guidance.

Because BP, CBF, and cerebral oxygen consumption vary directly with age, minimum CPP treatment thresholds have also been age-scaled.(5) The authors of the 2003 first edition of the “Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents”(6) proposed an age-related continuum of CPP thresholds between 40 (infants) and 65 (adolescents) mm Hg. The second edition of the guidelines, published in 2012, included the same minimum CPP threshold of 40 mm Hg, but the target for older children was adjusted downward to near 50 mm Hg based primarily on adult studies published in the interim.(1) Unfortunately, no studies to date have demonstrated that maintenance of CPP above a given threshold improves outcome in children of any age with TBI; however, White et al reported that supranormal BP is associated with improved outcome(7), and several case series have reported very high rates of mortality when CPP is persistently below 40 mm Hg.(8-10)

In this issue of *Pediatric Critical Care Medicine*, Allen et al[ref] report a retrospective analysis of prospectively collected data from the Brain Trauma Foundation (BTF) and New York State’s TBI-trac© database. The study was conducted between mid-2000 and mid-2008, and included adults, but we will focus our comments on the pediatric data reported. The purpose of the study was, in patients with a post-resuscitation Glasgow Coma Scale score < 9 without fixed and dilated pupils, to analyze the relationship between the age-specific CPP ranges recorded in TBI-trac© and 14-day mortality. No mention is made of patients who did not receive ICP monitors, although the TBI-trac© research group has recently published an analysis of adults with severe TBI with and without ICP monitoring. (11)

The CPP ranges in the database were based on BTF guidelines published in 2000(12), before the first edition of the pediatric guidelines, and were lower than current recommendations for young children but consistent with current recommendations for older children: 30-40 mm Hg for children < 6 years old, 35-50 mm Hg for children 6-11 years old, and 50-60 mm Hg for children older than 11. Patients were categorized into three exposure groups: 1) all recorded CPP's were above the target range (CPP-High), 2) all CPP's were within or above the target range but not below it (CPP-Between), and 3) any CPP was below the target range (CPP-Low).

Strengths of this study include the sample size, which at 317 children with severe TBI is very large, and the careful patient selection process, which excluded moribund patients unlikely to benefit from CPP-directed therapy. Allen et al found that children who had any recorded CPP's below the target range (< 30 mm Hg for those <6 years old or < 35 mm Hg for those 6-11 years old) had higher 14-day mortality than those who only had values in the target range or above it. This is perhaps not surprising, as those values are below the minimum CPP supported by level III evidence in both editions of the pediatric TBI guidelines. Interestingly, no mortality difference was seen between groups in children 12-17 years old, perhaps because the target range of CPP 50-60 mm Hg is less likely to contribute to ischemia at its lower end.

The authors also attempted to leverage the duration of the age-specific CPP values (high, between, and low) in the database using Kaplan-Meier analysis. However, those figures present mortality for the lowest CPP group that a patient achieved and do not account for a patient experiencing different CPP ranges at different times during the hospitalization. A more illuminating analysis might have shown the number of hours in each CPP category for each patient and then analyzed the impact of time, in hours, below currently recommended thresholds (40 mm Hg in the youngest patients and 50mm Hg for all other patients) on mortality. This type of analysis would come closer to the "pressure-time index" analyses reported by Adelson et al(13) and Chambers et al.(14) If the mechanism by which CPP-guided therapy affects outcome is prevention of ischemia, the ideal summary statistic would incorporate both the degree of ischemia (CPP) and the amount of time spent ischemic. The authors of the 2012 pediatric TBI guidelines recognized the variability of CPP summary statistics as a challenge to be overcome in future studies.(1)

Allen et al identified limitations to their study including that the various centers in TBI-trac© recorded CPP measurements at different frequencies and did not describe how they handled brief ICP spikes associated with care such as endotracheal tube suctioning. These limitations may have contributed to misclassification of exposure groups. The potential variance between ICP values recorded by an intraparenchymal fiberoptic monitor versus an external ventricular drain depending on patient size and bed angle, another challenge identified by the guidelines' authors(1), was not captured in the present study.

CPP-guided therapy is widely used despite its limited evidentiary base. Similarly, jugular venous bulb oxygen saturation and brain tissue oxygen monitoring do not yet have robust evidence that they improve outcomes in children with TBI(1, 15), but using them to more

accurately titrate cerebral oxygen delivery is an attractive concept to be tested in future studies.

Overall, this study strengthens the medical evidence regarding minimal CPP goals for younger children and that exposure to CPP < 35 mm Hg is associated with increased mortality. However, it cannot answer whether medical management to provide age-appropriate CPP ranges improves hospital survival. Nonetheless, TBI-trac© is a unique and rich data source, and we look forward to future analyses using this information.

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