Neurocrit Care (2021) 35:613–614
https://doi.org/10.1007/s12028-021-01307-z

NEUROCRITICAL CARE SOCIETY

INVITED COMMENTARY

Making Waves: Will It Help Children with Traumatic Brain Injury?

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Standardized patient care through a steady evolution of protocols, guidelines and care bundles has improved survival from disease. With improved survival, the focus has shifted to reducing morbidity and improving quality of life, especially in children as the survival even after critical illness is more than 95% [1, 2]. The more recent clinical trials using fixed protocols and treatment bundles in patients who are critically ill have failed to show improved outcomes despite many similarities in the expected illness trajectory and physiological response associated with a specific disease challenging the idea of universal application of standardized treatment protocols [3]. The idea that "one size may not fit all" is gaining popularity in the scientific community acknowledging the variability in both the host and the disease [3]. In addition to maintaining standard of care, there is a growing need to personalize treatment for the patient and the dynamic disease process.

One such disease that demands urgent attention is traumatic brain injury (TBI) which leads to significant morbidity in the survivors [4]. Recently published international guidelines for management of TBI in children recommend maintaining intracranial pressure (ICP) less than 20 mmHg and cerebral perfusion pressure (CPP) between 40 and 50 mmHg [5]. The changing physiology in the pediatric age group with changes in ICP and cerebral blood flow (CBF) throughout maturation from the neonatal period to adulthood means that these targets are inadequate across the pediatric age range. It is therefore important for us to find methods to individualize treatment targets for children [6].

Cerebral Autoregulation (CA) has gained importance as a treatment target in adult TBI guidelines and is gaining popularity within pediatric practice [7]. The state of CA has shown an association with the outcome in children following both mild and severe TBI, mainly in retrospective and single centre studies [8, 9]. Although both static and dynamic methods have been used to study the state of CA in children, there is growing support for use of model-based indices of CA in children which offer the advantage of continuous real-time dynamic assessment of CA [10]. Various different model-based indices have been developed by studying correlation between continuously monitored ICP with a surrogate of cerebral blood flow (CPP, Mean arterial pressure (MAP), regional oxygen saturation (RSO_2), Brain tissue oxygen tension ($PbtO_2$), Doppler flow velocities of intracranial arteries etc.) which define the state of CA [10]. The last two decades have seen evolution of optimal CPP (CPPopt) as the most promising and thereby most extensively studied potential treatment target using these indices [11]. Retrospective studies have shown association of the wider difference between CPP and CPPopt with worse patient outcomes and subsequent hypothesis that the outcome may be improved by maintaining CPP close to CPPopt. The CPPopt is also used to derive lower and upper limits of autoregulation (LLA/ULA) which can potentially define the limits within which CPP should be targeted in an individual patient. The much-anticipated results from a phase II trial COGiTATE (CPPopt Guided Therap: Assessment of Target Effectiveness) studying CPPopt based treatment will help understand further whether this could be used to improve neurodevelopmental outcomes [12]. Much of the construct of CPPopt depends on the U-shaped curve fitting against the measured pressure reactivity index values (PRx- moving correlation coefficient of slow wave fluctuations between ICP and arterial blood pressure). This has been further expanded by using phase shift between the two waveforms to derive wavelet PRx (wPRx) which yields better fit for the U-shaped

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curve and more consistent calculation of CPPopt for treatment use [13].

In this issue, Appavu et al. [14] have published their experience of using these model-based indices of CA in children with severe TBI. Appavu's study is novel in being the first to study the association of these relatively newly established indices of CA (PAx and wPRx) in pediatric TBI. They have compared the association of different model-based indices and dose of intracranial hypertension (dICH) with the 6-month global neurological outcome as assessed by Glasgow Outcome Score Extended Pediatric Revision scores (GOSE-Peds). They are also the first to calculate CPPopt from each of these indices, along with LLA and ULA. They have then calculated the percentage of time spent below or above LLA and ULA, respectively, to see if that had any impact on outcome. The most interesting finding was that the increased time spent below LLA, as calculated by wPRx, was the sole independent predictor of higher GOSE-Peds scores at 6 months in children < 2 and > 8 years of age, and that dICH was more strongly associated with outcome prediction in children 2–8 years old. The authors have hypothesized that this variation is due to changing CBF dynamics in the children 2–8 years. This is important at the patient's bedside, as practically targeting a range (between LLA and ULA) is more achievable than a single number (CPPopt) and will help in designing interventional studies.

There are few points that need further evaluation. The calculation of CA indices and dICH is based on the dynamics of a closed intracranial compartment, and we know from previous evidence that the application of these can be flawed in patients who have undergone decompressive craniectomy; the current study had 37.5% of patients who underwent decompressive craniectomy, and it will be important to study this group separately to understand the application of these indices in this cohort of patients. Given this logic, it is equally important to understand how this applies to children with open fontanel. Hopefully, ongoing studies of advanced cerebral hemodynamics will clarify some of these questions, and in the future, we may be able to use protocolized treatments based on individualized targets calculated from these indices. Meanwhile, this study is an important endeavor toward understanding CA in relation to CPPopt and the limits (LLA, ULA) and individualizing targets in TBI management in children.

Source of support
No funding was provided for this work.

Conflict of interest
The author declraes that thay have no conflict of interest.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 16 June 2021 Accepted: 18 June 2021
Published online: 15 July 2021

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