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ARTICLE OF THE MONTH

Differing Effects When Using Phenylephrine and Norepinephrine to Augment Cerebral Blood Flow After Traumatic Brain Injury in the Immature Brain

Friess SH, Bruins B, Kilbaugh TJ, Smith C, Margulies SS
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For the April 2015 SNACC Article of the Month, we have selected an article which is translational in nature, but has very important clinical implications for trauma in the developing brain. The article by Friess *et al*. is a study comparing the varying hemodynamic and chemical effects of phenylephrine and norepinephrine in a 4-week old swine model of traumatic brain injury. The parameters compared between the two cohorts included ICP, CBF, $PbtO_2$ (brain tissue oxygen tension), and markers obtained by microdialysis (lactate/pyruvate). As pointed out in the commentary below, the swine model used is a significant advantage over previous rodent models used to study similar outcomes. This is an important undertaking because vasopressor choice in the setting of pediatric traumatic brain injury, up until now, has been largely empiric and goal-directed only in the sense of attaining a predetermined CPP. The other parameters which were investigated in this study are of huge clinical importance. To shed an expert light on this paper, we have enlisted the help of William Armstead, PhD, from the University of Pennsylvania, who is a Professor Anesthesiology and Critical Care and Pharmacology, and truly an authority on cerebral hemodynamics during pathologic brain states. We thank you for your interest in this article, we hope you enjoy reading the article and commentary below, and we ask you to share your thoughts with us via the ***SNACC LinkedIn Feed***.

~John F. Bebawy, MD

Commentary

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Trauma is the leading cause of child death, and traumatic brain injury (TBI) is the leading cause of pediatric trauma related death. When caring for injured children, surgeons, anesthesiologists, emergency medicine physicians, and intensivists often struggle to prevent and expediently correct the unwanted but prevalent hypotension. This is problematic because systemic hypotension leads to low cerebral perfusion (cerebral perfusion pressure [CPP] and cerebral blood flow [CBF] that results in cerebral ischemia and poor outcomes. Current Level II recommendations are to maintain systolic blood pressure > 70 + 2 (age) and if ICP monitoring

occurs, to maintain CPP above 40 mmHg, but noting that an age-related continuum for the optimal CPP is between 40 and 65 mm Hg. Maintaining CPP within these levels is often managed by use of vasopressors to increase CPP and optimize CBF. Because of the paucity of data, there are no recommendations on the most effective vasopressor. Thus, choice of vasopressor agent is largely empiric, and variable. Importantly, vasopressor agents, such as phenylephrine (PHE), norepinephrine (NE), dopamine (DA) and epinephrine (EPI), while clinically used to elevate blood pressure, have not been compared vis-à-vis their effect on cerebral outcomes (hemodynamics [CPP] and perfusion [CBF]) after trauma.

Although several rodent models of TBI have been described, all have the disadvantage of not permitting repeated measurements of systemic physiological variables and regional CBF because of the small size of the subjects. Additionally, rodents have a lissencephalic brain containing more grey than white matter. In contrast, pigs have a gyrencepahalic brain that contains substantial white matter similar to humans, which is more sensitive to ischemic damage than grey matter. A number of neuroprotectants identified in preclinical rodent stroke and TBI studies have yielded disappointing results when entered into clinical trials. We speculate that the reason for failure may rest on these drugs being primarily grey matter protective owing to the greater amount of grey compared to white matter in the rodent.

Recognizing the translational importance of the pig, Dr. Friess and colleagues *(J Neurotrauma* 32: 237-243, 2015) determined the injured brain's response to phenylephrine (PE) and norepinephrine (NE) by measuring the cerebrovascular physiology and short-term neuropathology of four-week-old juvenile/young adult female pigs subjected to nonimpact inertial brain injury. The authors chose to compare these two vasopressors because a prior retrospective study of pediatric patients with severe TBI observed that PE and NE were found to be the most common vasopressors utilized, and post analysis did not reveal any significant differences in cerebral dynamic responses between the two vasopressors. In the present studies, a CPP of 70 mm Hg was targeted, because recent studies from the Friess group reported that increasing CPP to that level with PE resulted in greater reduction in metabolic crisis and cell injury volumes that targeting a CPP of 40 mm Hg. After initiation of CPP augmentation with PE or NE infusions, there were no differences in ICP between the groups over time. Animals receiving NE had higher brain tissue oxygenation than those receiving PE. CBF increased similarly in both PE and NE groups but the lactate/pyruvate ratio and cell injury volumes were less in those given PE compared to NE. In the context of the neurovascular unit, blood flow is thought to contribute to brain cell integrity. Since the authors assessed both traumatic axonal injury volume by determination of beta amyloid precursor protein and cell injury volume by H & E, these data show that PE limited white matter damage after TBI, a key translational index of improved outcome. However, the experimental observations in this study are somewhat perplexing in that cell injury was more marked with use of NE despite similar CBF in NE and PE animal groups. A potential explanation may be that reductions in mitochondrial function might account for less oxygen utilization and more hypoxic ischemic injury with use of NE compared to PE.

There are some other key points. This study used female pigs and unrelated studies have observed that PE CRI improved CBF after TBI in female but not male piglets, indicating the possibility for sex dependent differences in outcome despite achieving equivalent targeted CPP in males and females. Additionally, this study used young adult pigs and prior studies comparing newborn one- to five-day-old and four-week-old young adult pigs observed greater reductions in CBF after equivalent intensity TBI in newborn compared to young adult pigs, indicating that the pediatric age group is much more sensitive to brain injury. Further, mechanisms for impaired cerebral hemodynamics differed as a function of age and sex. Based on cross species brain maturation curves, translationally the newborn pig approximates the age range for shaken impact, whereas the four-week-old pig may better approximate the injury seen in young adults such as motor vehicle accident. Taken together, these data argue for consideration of sex and age dependent differences in determining the best therapeutic approach in treatment of TBI. Future clinical studies comparing the effectiveness of various vasopressors for CPP support are warranted.