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Pediatric traumatic brain injury: is it time to consider gender-based treatments?

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Traumatic brain injury (TBI) remains a leading cause of death from injury in children (1) despite advancements in neuromonitoring and treatment modalities. Impairments in cerebral autoregulation and vasoreactivity with low blood pressure are associated with worse outcomes in pediatric TBI (2, 3). The Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents from 2012 provide a level III recommendation to maintain cerebral perfusion pressure (CPP) at 40 mmHg or higher, with recognition that age influences the range of blood pressure at which autoregulation is supported (4). However, we do not have adequate evidence to guide *how* we should support our patients' blood pressures after TBI. Clinicians vary considerably in how they support CPP (5). The choice of vasopressor may be partially driven by whether the patient needs inotropic support for concomitant cardiopulmonary injury, in addition to vasopressor support. Institutional preference and local clinical protocols are also driving factors. When faced with a hypotensive child who has suffered TBI, should we use phenylephrine, norepinephrine, dopamine, or a combination with volume resuscitation?

Because gender affects the risk of suffering TBI (6, 7) and the subsequent outcomes (8, 9), we must consider whether boys and girls should be treated differently. Tailoring therapeutic interventions to our patients' characteristics, most notably gender, could improve outcomes after TBI. Indeed we have growing evidence that gender and hormonal influences affect outcomes after TBI (10) and alter responses to vasopressors after brain injury (11).

Armstead and colleagues (12) have begun to address these questions using a clinically relevant piglet model of TBI with fluid percussion injury. Piglets were randomized to receive norepinephrine infusion or no vasopressor support after brain injury. The investigators targeted a CPP of 55–60 mmHg using norepinephrine or fluid boluses as needed, and the resulting CPP was similar among experimental groups. Cerebral

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autoregulation was then tested during conditions of transient hyperemia (compression of the carotid artery) and hypotension (withdrawal of blood to attain moderate or severe degrees of hypotension). During responses to transient hypertension, norepinephrine maintained autoregulation only in females; male piglets showed impaired autoregulation with norepinephrine. When autoregulation is intact, cerebral arteries should dilate in response to hypotension, thereby maintaining cerebral blood flow and preventing ischemia. The investigators found that impairments in pial artery dilation during hypotension were more severe in males than in females. The addition of norepinephrine restored the pial artery dilation response to hypotension in females, indicating a restoration of autoregulatory function, but failed to restore the vasodilation response to hypotension in males. Thus, autoregulation remained impaired in the male piglets. The observed gender-dependent effects of norepinephrine on autoregulation may be mediated by the ERK isoform of mitogen-activated protein kinase and interleukin-6.

To correlate cerebral blood flow autoregulation measures with cell death, the investigators conducted a histologic analysis of hippocampal neurons. The number of necrotic neurons in the hippocampus was greater in males than in females after brain injury. Norepinephrine increased the severity of neuronal necrosis in males but preserved hippocampal neurons in females. Thus, the investigators provide evidence that impairments in cerebral autoregulation and hippocampal neuronal injury—as well as their response to norepinephrine—differ between males and females after TBI. However, the influence of gender appears to depend on the type of vasopressor used. This same research group has previously shown that dopamine protects autoregulation after TBI in both male and female piglets (13).

Although critics may argue that piglets are not humans, the piglet brain is remarkably similar to the human newborn brain in terms of development and regional vulnerability to injury. Therefore, the piglet model is well suited for the study of pediatric brain injuries, derangements in cerebral blood flow, neuronal injury, and responses to treatments. We must pay close attention to translational laboratory studies that may shed light on how we can improve clinical treatment for pediatric TBI. Gender is often overlooked as an influencing factor in TBI outcomes, but its importance should not be understated.

Research in the treatment of TBI increasingly illustrates the importance of supporting CPP to maintain cerebral autoregulation. Cornerstone to autoregulation-oriented treatments is the avoidance of hypotension. Whether clinicians should use norepinephrine, dopamine, phenylephrine, or another vasopressor alongside fluid boluses is the subject of much debate. But what cannot be debated is that we must prevent hypotension in children recovering from TBI. Additional research is needed to discern the safest and most effective methods of achieving this goal. The evidence provided by Armstead, et al. (12) in a piglet model, that norepinephrine may be beneficial to females recovering from TBI but harmful to males, must be considered carefully by clinicians. While we are many steps away from clinical trials designed to test different vasopressors in pediatric TBI, Armstead et al. bring our attention to the urgency of this question and the importance of controlling for gender when designing such trials.

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