Letter: Development of a Randomized Trial Comparing ICP-Monitor-Based Management of Severe Pediatric Traumatic Brain Injury to Management Based on Imaging and Clinical Examination Without ICP Monitoring-Study Protocol

To the Editor:

Pediatric traumatic brain injury is a major public health concern, particularly in resource-limited settings where this entity has higher incidence and mortality than developed nations. Despite the disproportionate burden of pediatric traumatic brain injury in low- and middle-income countries (LMICs), the current Brain Trauma Foundation guidelines are largely based on low-quality evidence generated in high-income countries (HICs).[1] Adherence to guidelines is challenging in LMICs because of economic constraints, equipment availability, and human resources,[2] which may explain disparities in outcomes. We applaud Chesnut et al[3] for publishing a randomized controlled trial (RCT) protocol to test the hypothesis of whether intracranial pressure (ICP) monitoring improves outcomes in pediatric severe TBI (psTBI). The RCT will compare outcomes for children receiving ICP-based vs clinical examination and imaging-based management. Their main objective is to generate class I evidence regarding the impact of ICP-driven management in psTBI on long-term outcomes.

Current Brain Trauma Foundation guidelines for psTBI recommend ICP monitoring to guide treatment, acknowledging that high-quality studies evaluating the impact of neuromonitoring are needed.[1] Although this RCT will compare outcomes for children with and without ICP monitoring, the authors argue that this study is not evaluating the value of knowing the ICP but the efficacy of protocol-based treatment. Because many trauma centers in LMICs rely on clinical examination and imaging-based protocols to guide management for sTBI because of lack of availability of ICP monitoring, the authors state that there is equipoise as to whether ICP monitoring should be used in these settings.

Many ethical questions arise regarding justification of this RCT in four Latin American countries: El Salvador, Guatemala, Honduras, and Perú. If equipoise exists to study the clinical value of ICP monitoring (and we might agree that this is the case), why is this National Institutes of Health (NIH)-funded trial being conducted only in settings where ICP monitors are not routinely placed because of lack of resources and trained personnel? Although a large retrospective study showed that children with sTBI managed with and without ICP monitors had no difference in functional outcomes,[4] ICP-driven management of psTBI remains the standard of care in HIC. To ethically justify randomizing children to receive management other than the standard of care, the entire medical community, not only that in certain parts of the world, must agree there is equipoise between the two management strategies.

Conducting research in LMICs that would not be ethically justified in HICs creates a double standard for evaluating the risk-benefit ratio for research participants.[5] The BEST TRIP trial that evaluated the impact of ICP monitoring on outcomes in Latin American adults received similar criticism.[6] Children, especially those in LMICs, represent a vulnerable population and require additional protections to ensure their safety in research studies. Stating there is equipoise only in LMICs and deferring the study's risk-benefit evaluation to participating sites implies that children in different parts of the world deserve different research protections. The Global Code of Conduct for Equitable Research Partnerships states that research should not be conducted in LMICs if it would be restricted in HICs unless the disease or condition being studied is uncommon in HICs.[7] Pediatric sTBI affects children globally, so we argue this NIH-funded research should include children from HICs and LMICs so that its potential risks and benefits are shared among children globally.

If the authors' hypothesis proves to be false, will the authors propose changing practice worldwide to replace ICP-based protocols with clinical examination and imaging-based protocols? Providers in HICs are often hesitant to withhold therapies, even when evidence suggests they are ineffective. The BEST TRIP trial found no difference in functional outcomes for adults with sTBI receiving ICP-monitor directed therapy or tiered medical therapy.[6] Results were criticized because of unusually high mortality rates in both treatment groups and have not been incorporated into clinical practice in HICs. In fact, HICs continue to evaluate the ability of ICP-monitor driven protocols to improve outcomes for adults with sTBI.[8]

There is value in exploring whether high-cost therapies, such as ICP monitoring, should be implemented in settings that lack those resources. A stepped wedge, cluster randomized trial that includes sites currently lacking ICP-monitoring capabilities could answer this question in a less ethically controversial way.[9] Although this design is subject to more bias than a traditional RCT, it would accomplish two similar goals: (1) compare outcomes for children with sTBI receiving ICP-based vs clinical and imaging-based management and (2) increase global capacity for pediatric neurocritical care. Given that 80% of child deaths worldwide occur in LMICs, improving access to critical care resources and trained personnel is essential to reduce global disparities in child health and well-being.

We thank the authors for publishing their RCT protocol before starting the study so the academic community can discuss these controversial topics. If equipoise exists between ICP-monitor driven management and clinical and imaging-based management in children with sTBI, we encourage authors to expand this

RCT to include children from HICs and LMICs so that all children with sTBI share its risks and benefits. If not, how can the global community ensure that the most vulnerable children in LMICs are protected from excessive risk and potential harm in international multicenter clinical trials?

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