Hypotension in Traumatic Brain Injury: Describing the Depth of the Problem

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Out-of-hospital hypotension is detrimental to patients with traumatic brain injury,[1,2] yet the optimal out-of-hospital management of traumatic brain injury remains elusive. For years, avoidance of systolic blood pressure less than 90 mm Hg has been the sole hemodynamic recommendation for out-of-hospital traumatic brain injury care, based on a single study of 717 subjects.[3] Spaite et al[4] recently clarified that hypotension has a dose-response effect, with deeper hypotension associated with increased mortality. Yet traumatic brain injury mortality cannot be simply a function of a single discrete blood pressure measurement; the *duration* of hypotension must surely influence traumatic brain injury outcomes.

In this issue of *Annals*, Spaite et al[5] build on this body of knowledge, showing the effect of, and interaction between, depth and duration of hypotension on mortality. This secondary analysis of the Excellence in Prehospital Injury Care (EPIC) study challenges the simplistic dichotomy of "good" and "bad" blood pressures, identifying that a doubling of the hypotension "dose" (depth×duration) is associated with a 19% increase in inhospital mortality. Currently, providers may be more likely to treat hypotension only when it is associated with overt shock and even allow permissive hypotension in the setting of multisystem trauma.[6] Yet Spaite's new study suggests that both severe hypotension of brief duration and prolonged low blood pressure may be associated with poor outcomes, highlighting that the relationship is not as simple as a dichotomous concept of "hypotensive or not."

The opportunity to affect patient outcomes is substantial and may include patients not previously considered as hypotensive. Normal or elevated mean arterial pressure supports an adequate cerebral perfusion pressure, especially in patients with increased intracranial pressure. Hypotension (systolic blood pressure <90 mm Hg) was observed in 7% of patients with traumatic brain injury in this study.[5] However, previous analyses of the EPIC study group demonstrated increased mortality in patients with traumatic brain injury who were exposed to a minimum out-of-hospital blood pressure as high as 135 mm Hg.[4] Using a systolic blood pressure cutoff of less than 100 mm Hg or even higher would represent a larger cohort of patients exposed to relative hypotension who may benefit from treatment. Thus, patients with traumatic brain injury may benefit from interventions that improve cerebral perfusion pressure across a range of blood pressures that are not traditionally considered hypotensive.

How do we use these data to inform traumatic brain injury treatment? Spaite's linear relationship between the $\log_2$ dose and log odds of death cannot be easily determined by paramedics in real time. To use hypotension dosage data, emergency medical services personnel may require real-time decision support tools that calculate the cumulative hypotension dose. Although monitor software could be designed to alarm once a dose threshold has been reached throughout the range of blood pressures, this technology does not currently exist.

We must remember that when assessing the full cohort, Spaite et al observed no change in the net reclassification improvement, suggesting no prognostic advantage of hypotension dose over binary systolic blood pressure across patients with traumatic brain injury. Thus, a sensitivity analysis of systolic blood pressure is necessary to identify measures that could better predict traumatic brain injury mortality. We may ultimately discover that use of a simple dichotomous threshold (say, <100 or <110 mm Hg) would be accurate and easier to monitor and implement. Which model should be used and at what threshold remain unanswered and beg further study.

Hypotension must not be considered in isolation; hypoxia and hypocarbia may also affect traumatic brain injury outcomes.[1,2] If we accept hypotension dose as the best available field measure of cerebral hypoperfusion, then

interactions between hypotension, hypoxia, and hypocarbia likely effect a collective influence on brain tissue oxygenation. This may cause unintended consequences because focus on one parameter may adversely influence another factor, leading to a net negative effect. For example, intubation may result in exposure to hypoxia during the procedure and hypocapnia after airway establishment.[2,7] Administration of sedatives to facilitate intubation in the field may worsen hypotension and eliminate any positive effects of improved oxygenation. Similarly, if the only available treatment for patients with hypotensive multisystem trauma and traumatic brain injury is large-volume crystalloid infusion, then dilution of clotting factors, worsening acidosis, and increased bleeding may negate the benefit of improved cerebral perfusion pressure. Monitor-based decision support tools integrating blood pressure, pulse oximetry, and continuous capnography data may be necessary to guide traumatic brain injury care.

Consider that the EPIC studies reflect observational *associations*. We do not know whether avoidance or reversal of hypotension directly affects outcomes. Ultimately, clinical trials are needed to answer this key question. Such trials might randomize patients to actionable thresholds of 90 versus 110 mm Hg or resuscitation with volume versus vasopressor agents. So far, out-of-hospital studies of intubation and hypertonic saline solution have not been able to demonstrate improved outcomes[8,9]; whether management of hypotension can improve traumatic brain injury outcomes remains unanswered. An interventional trial evaluating the implementation of out-of-hospital guidelines for traumatic brain injury management is currently under way in the EPIC study, focusing on optimizing oxygenation, ventilation, and management of hypotension (systolic blood pressure <90 mm Hg for adults).[10] Additional interventional trials will be needed to test treatment algorithms based on other systolic blood pressure cutoffs or the hypotension dose, as well as composite measures of hypotension, hypoxia, and hypocarbia. Now that we have a deeper understanding of the complex association between hypotension and traumatic brain injury, we must learn how to intervene and improve outcomes.

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