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Intracranial pressure monitoring: headstone or a new head start. The BEST TRIP trial in perspective

R. M. Chesnut
Harborview Medical Center, University of Washington, Seattle, WA, USA, chesnutr@uw.edu

Intracranial pressure (ICP) monitoring is considered the standard of care for severe traumatic brain injury (sTBI) and its use is suggested by guidelines [1]. The efficacy of treatment based on monitoring in improving outcome had not been rigorously assessed, however, until the recently published BEST TRIP study [2]. This was a multicenter, controlled trial in Bolivia and Ecuador in which 324 patients with sTBI were randomly assigned to one of two specific protocols: guideline-based management based on monitored ICP versus treatment based on imaging and clinical examination. The primary outcome was a composite of survival time, impaired consciousness, and functional status at 3 months and 6 months and neuropsychological status at 6 months. The trial found that care focused on maintaining monitored ICP at 20 mmHg or less was not superior to care based on imaging and clinical examination. A major concern of the authors was that misinterpretation of these results might lead to abandoning ICP monitoring in managing sTBI.

Proper interpretation of the BEST TRIP study [2] benefits greatly from examination of two aspects of the environment in which it was performed. The first reflects the confounding environment in which ICP first became clinically accepted and integrated into practice. The second is the actual state of evidence supporting the role of ICP-guided management in improving outcome. Prior to the advent of ICP-based management, TBI-specific intervention was essentially limited to surgery, applicable to only those patients in whom an intracranial mass lesion was suspected and demonstrated by the limited diagnostic tools of the pre-CT era (e.g. cerebral angiography). Following the introduction of ICP monitoring specific management became possible in all TBI patients and therefore prompting ICU admission. The increased medical scrutiny resulting from ICU admission brought with it improved general medical management, with the patients benefitting not only from treatment of ICP but other aspects as well, such as mechanical ventilation, careful fluid management, infection control, nutrition, etc. Over time, it also led to the introduction of specialist intensivists, some of whom have specific neurological training.

Contemporaneously, other critical developments augmented TBI management. CT scanning became generally available, finally affording precise anatomical diagnosis and making imaging available to all patients with suspected TBI. Care of trauma patients in general both before and after hospital admission evolved rapidly, with basic life support and advanced trauma life support training becoming widespread and the disciplines of emergency medicine and trauma surgery developing apace. Finally, aspects of resuscitation particular to TBI were undergoing revolutionary changes; in particular, the discarding of the “keep them

Correspondence to: R. M. Chesnut.

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dry" philosophy for aggressive fluid resuscitation. No longer was borderline hypotension the rule of the day.

Over the period between 1970 and 1990 when the above evolution was occurring, the outcome following severe TBI improved markedly. When adjusted populations are analyzed, the mortality rate over this period dropped by 9 % per decade, compared with no significant change between 1930 and 1970 or from 1990 to date [3]. Despite the tendency to invoke the acceptance of ICP monitoring and management as fundamental to this improvement, the correct analysis must concatenate the entire spectrum of advances noted above [4, 5]. Determination of the independent contribution of treatment based on ICP monitoring to outcome requires a randomized, controlled trial.

In 1995, Ghajar et al. [6] surveyed 261 US trauma centers, and found routine ICP monitoring at only 28 %. At the 1992 annual meeting of the Congress of Neurological Surgeons, Jam Ghajar, Don Marion and I were discussing these data prior to publication and expressed our belief that a proper evidence-based presentation of the literature on ICP monitoring and outcome would mandate widespread adoption. These ruminations, overheard and realized by Peter Quinn, then executive director of the Brain Trauma Foundation, resulted in that institution facilitating and funding the writing of the first edition of the guidelines for the management of sTBI in adults [7]. That work rigorously demonstrated that we had been wrong in our understanding of the literature in that there was very little evidence that ICP monitoring and management per se improved outcome and the available evidence was of low level. Unfortunately, this situation has maintained through the most recent (2007) revision [1].

In this light, the results of the BEST TRIP trial [2] seem less surprising; indeed, they might have been anticipated. Being the first brain-specific monitoring parameter in common use and being associated in aggregate with such improvements in TBI care and outcome, ICP monitoring had taken on the visage of the cornerstone in the field. Subsequent research into different treatment methods focused on their efficacy in altering ICP, rather than on their independent influence on outcome. Additional treatments and techniques (such as jugular venous oxygen saturation monitoring, brain tissue oxygen tension monitoring, cerebral dialysis, and numerous pharmacological agents) were instituted and studied on top of (rather than parallel with) the background of basic ICP treatment protocols that had become popularly accepted as a *conditiones sina quibus non* despite the absence of rigorous scientific support. It also became clinically acceptable to consider prognostic futility in the face of inability to control ICP below a widely adopted but weakly supported threshold of 20–25 mm Hg. The fundamental role and basic approach to ICP management had become a given.

There were dissenters but their level of evidence was also poor. Cremer et al. [8] retrospectively analyzed outcomes from two level I centers, only one of which used ICP monitoring. There was no control of or adjustment for different management protocols and risk adjustment between groups was incomplete. They reported similar outcomes between cohorts and that the group receiving treatment based on ICP monitoring had significantly greater values of treatments received and ventilator days. Shafi et al. [9] retrospectively studied the courses of 1,646 sTBI patients from the National Trauma Data Bank, dividing them into those receiving monitoring versus those managed without. They reported that the group managed based on monitored ICP did significantly worse in terms of mortality and degree of functional impairment at discharge. Unfortunately, they lacked detailed information on several key demographic confounders, neither controlled nor adequately described treatment protocols or the rationales used to decide on monitoring, and provided only very short-term follow-up. Although providing no more scientific rigor than the studies

supporting treatment based on ICP monitoring, these reports served to remind us of our evidentiary shortcomings.

As well documented in the Brain Trauma Foundation guidelines [1], there is strong correlative evidence that high ICP is associated with a higher likelihood of impaired recovery, which firmly establishes its value as a marker of disease severity. Also secure is the knowledge that the consequences of markedly uncontrolled intracranial hypertension, such as cerebral herniation or global ischemia, are similarly predictive of poor outcome. The issue of contention is whether maintaining monitored ICP below a universal threshold, as manifest in our current concepts and practices, improves recovery; not versus no treatment or treatment of marginal intensity but as compared to aggressive management delivered without monitoring ICP. It would be extremely problematic to suggest studying the efficacy of any form of ICP management against a natural history control group. As such, the actual question becomes a methodological one.

The BEST TRIP study did not test the value of monitoring ICP per se. Rather, it specifically compared two aggressive TBI management approaches, one of which was guided by ICP monitoring. It demonstrated that both provided satisfactory outcomes, both long-term (the pre-specified endpoint) and short-term (post hoc analysis). ICP monitoring was more efficient in terms of halving the number of treatments administered per patient and reducing the number of ICU days during which patients received TBI interventions. The immediate clinical implication is that both of these very aggressive approaches, employed as in the study, appear to be equally effective in the general ICU TBI population.

This study may be criticized on several fronts. The composite outcome is less intuitive than the extended Glasgow outcome score [10] but it has solid precedent in the literature [11] and its sensitivity halved the number of patients required to power the study. The setting in developing countries is also notable. The identification of hospitals in Latin America where sTBI was routinely managed without ICP monitoring and where there was a balanced view regarding its efficacy critically eliminated the ethical constraint that impeded doing an randomized controlled trial in high-resource countries. However, much less sophisticated prehospital care complicates admission demographics and the lack of rehabilitation and high postdischarge mortality confound long-term outcome analysis. Notably, however, these differences equally influenced both treatment groups, and the ICU demographics, treatment courses, and short-term (14-day) outcomes appear comparable to US and European situations. Therefore, although cautious interpretation is advised, these results appear applicable to sTBI management in both low- and middle-income as well as high-income countries.

Should we be surprised by these results? In the context presented above, the likely answer is no. The BEST TRIP study did not question the value of knowing the ICP. Its values as a quantitative guide to therapy in general, as a prognostic indicator, and as a research tool were not addressed. What it did reveal was that our apparently oversimplified concepts surrounding manipulating ICP do not produce improved recovery in the general sTBI population. One primary shortcoming is likely the unfounded acceptance of a single value (generally 20 mm Hg) as a treatment threshold for all patients throughout their course. The remarkably astute observations of Miller et al. [4] underscored as far back as 1977 the uncertainty of any threshold and the need for adaptability in treating ICP. If we accept that many patients do have a critical ICP threshold above which aggressive treatment is warranted, we might ask if the DECRA trial did not fail to find a positive influence of decompressive craniectomy (a very effective method of lowering ICP) because it employed a nonphysiological clinical trigger threshold pressure [12]. Widespread usage of an inappropriate threshold, which triggers aggressive treatment with potentially toxic agents

(e.g. surgery, high-dose barbiturates, etc.) could substantially confound any clinical sTBI study built upon such standardized protocols. Indeed, one might consider the possibility that the resulting statistical “noise” might have induced type II errors that caused us to miss significant effects in past studies such as those involving pharmacological agents [13]. Overtreatment is not trivial, and classification of patients as “ICP nonresponders” based on a nonphysiological threshold will not produce meaningful analyses.

The strongest clinical implication of the BEST TRIP trial is that we need to refine the role of ICP monitoring in sTBI management. Given its established ease and safety, we do not feel that diminished ICP monitoring should follow this report. Instead, clinical methods for interpreting ICP in the setting of individual patients must be developed. Different injury patterns, the evolution of the physical properties of the injured brain over the course of treatment, the influence of extracranial influences (e.g. intrathoracic pressures), patient age, variable cerebral metabolic demands, etc. certainly interact to influence the physiological impact of ICP. Considering other measurable parameters such as brain compliance, static cerebral autoregulation, cerebral perfusion pressure, cerebral blood flow, the local and global matching of delivery to demand, as well as the often underutilized neurological and pupillary examinations, should allow us to recognize when an ICP of 25 or 30 mm Hg might be cautiously accepted rather than lead to second-tier interventions. If we can develop analytic approaches allowing protocolizing such decision making, perhaps leading to more meaningful subclassification of injury types, the true value of ICP monitoring as part of a multimodality approach to targeted therapy should become apparent. The role of ICP monitoring will then be less of a Holy Grail approach to keeping pressures below 20 mm Hg and more akin to the use of echocardiography or cardiac output measurement in classifying and guiding the management of cardiac disease. As intensivists, we probably should be embarrassed that we are not at such a point in TBI management already.

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