Management of Severe TBI – A Review of Recent Literature

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INTRODUCTION

Traumatic Brain Injury (TBI) is the result of sudden trauma causing damage to the brain. TBI can occur when the head strongly and abruptly changes direction or contacts an object, or when an object penetrates the skull and brain tissue. (Figure 1 – TBI). CDC estimated that in 2010, TBI, alone and in conjunction with other injuries, accounted for approximately 2.5 million ED visits, hospitalizations, and deaths in the United States. Children aged 0–4 years, adolescents aged 15–19 years, and, most significantly, adults aged 75 years and older are the most likely to sustain a TBI and seek medical care[1]. The leading cause of non-fatal TBI in the U.S. is falls and the leading cause of TBI-related fatalities is motor vehicle accidents[2].

As a heterogeneous condition, TBI is conventionally categorized as mild, moderate, or severe. The most useful classification system is the Glasgow Coma Scale (GCS) which is based on level of consciousness as assessed by eye, motor, and verbal performance. A GCS score of 13 to 15 classifies a mild TBI, 9 to 12 a moderate TBI, and a score of 3 to 8 defines a severe TBI (sTBI). Each year, the direct and indirect medical cost of TBI is nearly $76.5 billion, with 90% directed at severe TBI[3].

Although little can be done to reverse the initial, or primary, brain injury caused by trauma, care is directed at stabilizing the patient and preventing further, or secondary, brain injury. Concerns of delayed non-mechanical damage include swelling, inadequate oxygenation, lack of autoregulation, and metabolic dysfunction. Elevated intracranial pressure (ICP), often the result of increasing mass effect from hematomas and contusions, diffuse cerebral edema, or hydrocephalus, is an important promoter of secondary brain injury and is associated with worse neurological outcomes in patients after TBI. Consequently, medical and surgical efforts attempt to normalize ICP in order to maintain cerebral blood flow and prevent parenchymal death. (Figure 2 and 3– ICPmonitor1 and 2). In the past 5 years, three landmark trials have explored the beneficence of three individual techniques for mitigating secondary brain injury associated with intracranial hypertension. Although the following investigations do not isolate and then evaluate ICP treatment, they do smear the guidelines of practice for approach and management of sTBI.

DISCUSSION

BEST TRIP: A call for greater investigation into the efficacy of ICP Monitoring

For decades, ICP monitoring has been considered the gold standard for steering treatment in patients with sTBI. Despite guidelines, there is a great deal of variation in its use and patients may undergo ICP modification without the use of a monitor. (Figure 4 – ICP monitor 3). Only recently has the efficacy of direct monitoring on outcome improvement been explored by more than observational and nonrandomized studies. The Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST TRIP) trial was a multicenter, prospective RCT that enrolled 324 sTBI patients 13 years of age or older from four ICU's in Bolivia and Ecuador. Participants were randomized to one of two management strategies determined either by ICP monitoring maintaining ≤20mmHg or by clinical examination and serial computed tomography (CT) imaging[4]. The overall composite outcome was calculated as the average of percentiles from 21 measures, including survival time, duration and level of impaired consciousness, functional status at 3 and 6 months, and cognitive status at 6 months, with lower percentiles representing worse outcome. This five-year investigation demonstrated no statistical difference in overall outcome between the two groups (56% composite for pressure monitoring group vs. 53% composite for imaging-clinical exam group; p = 0.49). Six-month mortality, median length of stay in the ICU, and distribution of serious adverse events were also not significantly different.[5] These results suggest that clinical findings and imaging are sufficient for practitioners to determine a treatment regimen.

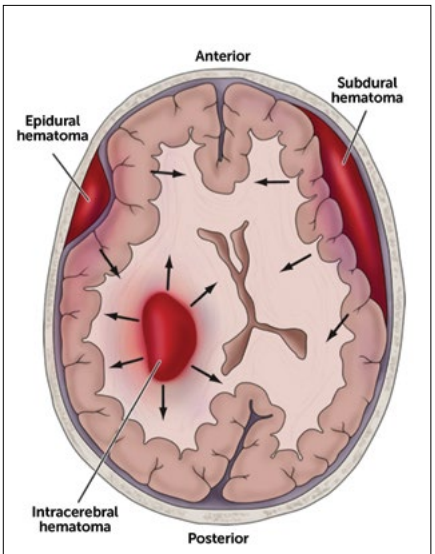

Figure 1.
TBI

However, the ability to generalize these findings and extend them to practice in developed countries is questionable. BEST TRIP was conducted in Bolivia and Ecuador; prehospital care is not as advanced as in higher income countries and rehabilitation is essentially non-existent. Severely injured patients in the sampled nations do not survive long enough to reach a care facility; consequently, sTBI cases represented in this trial are likely less severe than those seen in the U.S.[6] ICP monitoring may in fact assist in approaching treatment of more severe patients and this study could not include that population. Elderly patients, the largest contributors to sTBI care in the U.S., were also missed. Accurate information on prehospital interventions or early secondary insults such as hypothermia and hypoxia were not recorded or assessed in both transfer patients and trauma patients[7].

It is important to note that the BEST TRIP study did not intend to question the value of knowing the ICP and actively managing brain edema. What this trial did reveal was that our understanding of ICP manipulation is oversimplified and does not produce improved recovery in a general sTBI population[8]. For instance, a universal threshold of 20mmHg was used as recommended; in light of the study's findings, monitoring may be productive if this number could be personalized beyond the current standardized value. Overall, the strongest clinical implication stemming from the BEST TRIP trail is the need to refine the role of ICP monitoring in sTBI management, determining when it is efficacious and how to guide therapy based on its findings.

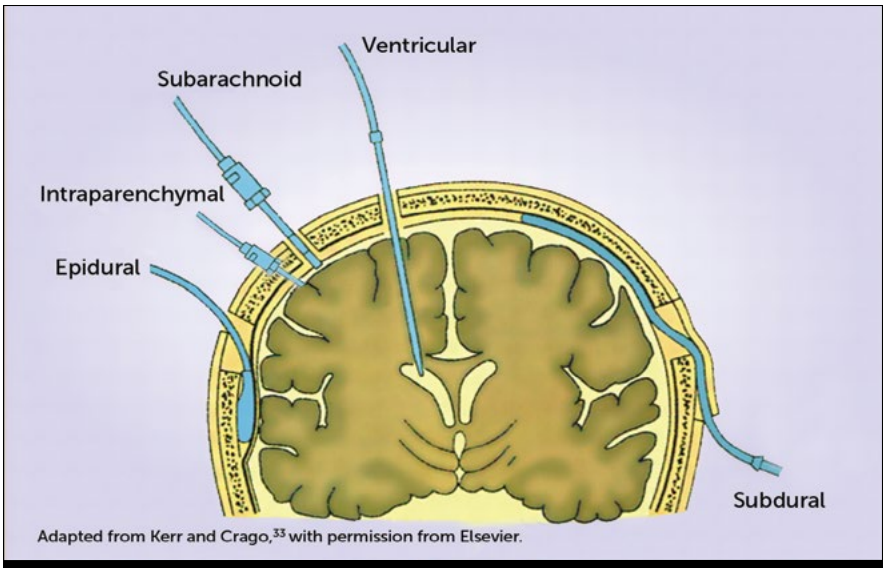

Figure 2.
ICP monitor 1

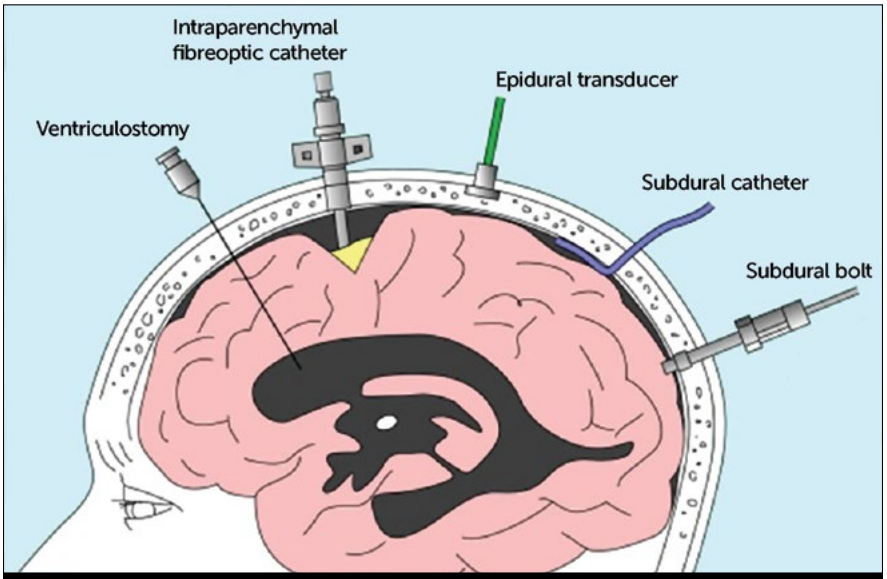

Figure 3.
ICP monitor 2

DECRA: Questioning the putative benefits of decompressive craniectomy

When patients with severe head injury have raised ICP that is refractory to first-tier therapies such as hyperosmolar infusions, surgical decompressive craniectomy (DC) is recommended. This procedure has been increasingly performed in the last 15 years and only recently has a randomized control trial taken place to explore its efficacy. The Decompressive Craniectomy (DECRA) Trial was conducted over eight years in fifteen ICUs in Australia, New Zealand, and Saudi Arabia to evaluate the impact of this optional approach on clinical outcome. Investigators assigned 155 adults between 15 and 59 years of age with severe diffuse TBI and refractory intracranial hypertension to receive either bifrontotemporoparietal decompressive craniotomy with standard care or standard care alone. The clinical outcomes were measured 6 months after injury using the Extended Glasgow Outcome Scale (GOS-E). Although the surgical group did demonstrate a significant decrease in ICP, fewer interventions,

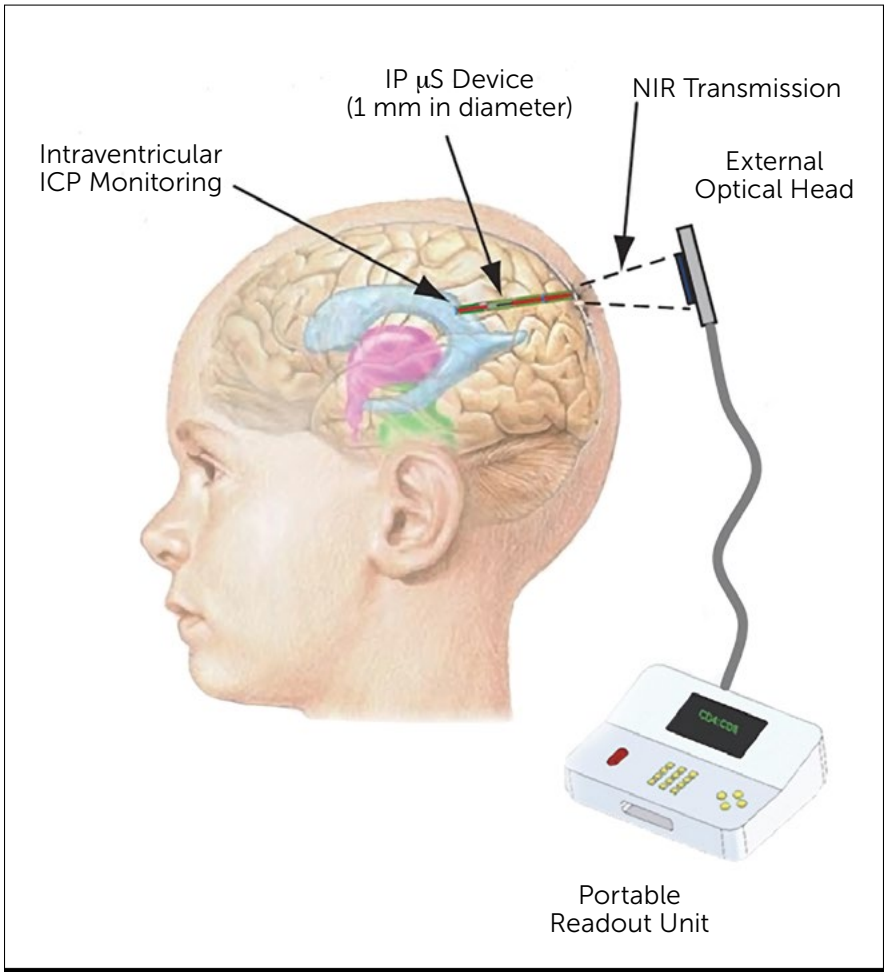

Figure 4.
ICP monitor

and a reduced length of stay, clinical outcomes were worse in the surgical group versus the standard-care group (70% versus 51%; p=0.02)[9]. The authors speculate axonal stretch, alterations in cerebral blood flow and metabolism, or complications of a bilateral approach as potentially relevant to these unexpected findings.

There are once again concerns of applicability raised by this study. Investigators enrolled only 155 patients despite the screening of 3478 patients, suggesting that the results are limited to a specific subpopulation. Further, the aggressive approach of a DC is typically not considered in patients with the guideline-based, standardized parameters used in this trial: ICP above 20mmHg for over 15 minutes despite medical therapy. Decompressive craniectomy is used as a last resort and DECRA may have included patients that are not typical candidates. There were also two exclusion criteria that may serve as points of contention: patients needing a unilateral DC and patients with previous evacuation of a mass lesion; in a multicenter study of 729 patients, it was found that about one third of patients receiving removal of an intracranial hematoma also required a typically unilateral decompressive craniectomy[10]. An important patient type was neglected from this evaluation.

Regardless of potential limitations, the DECRA study offered convincing support that early neuro-protective bifrontal DC is not superior to medical management for patients with severe diffuse TBI. Two more trials are currently underway – RESCUE-ASDH – and RESCUEicp – evaluating the efficacy of primary and secondary DC, respectively, and the parameters outlined seem more accurate and applicable[11]. In light of the currently available findings and the potential complications associated with DC, use of DC for patients with severe diffuse TBI should continue to remain highly selective.

Eurotherm3235: An unexpected response to therapeutic hypothermia

Elevated body temperature following brain trauma is associated with increased cytokine release and worsening of outcome. Given this as well as the neuro-protective effect of induced hypothermia after global brain ischemia caused by cardiac arrest, neonatal asphyxia, or drowning in cold water, hypothermia has become routinely used in some ICUs to treat elevated ICP in patients with TBI. However, its effect on outcome in this context has limited evaluation. The European Study of Therapeutic Hypothermia (32–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (Eurotherm3235) randomized 387 patients at 47 centers in 18 countries to receive standard care or standard care plus therapeutic hypothermia. Temperature was adjusted to maintain ICP at or below 20mmHg, and treatment continued for at least 48 hours as needed. The primary outcome measure was the score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months after injury. GOS-E score of 5 to 8, indicating moderate disability or good recovery, occurred less often in the hypothermia group than in the control group (25.7% vs. 36.5%; P=0.03)[12]. The occurrence of serious adverse events and mortality also favored the control group. Importantly, hypothermia-induced reduction of ICP had a similar efficacy as standard medical protocols.

The study's findings are implying a contraindication of active hypothermia in ICP management. However, there are important considerations raised by study critics. The Eurotherm3235 trial was terminated early due to safety concerns. Additionally, a lack of blinding

to the intervention, problematic in any trial involving therapeutic hypothermia, may have introduced bias[13]. Participants receiving hypothermia treatment may have more often reported serious adverse events, while control group participants expected these results. In regards to study design, investigators used an intracranial pressure of 20 mm Hg as a treatment threshold, but many protocols also measure cerebral perfusion pressure; intracranial pressures of up to 25 mm Hg may be safe provided that cerebral perfusion pressure is maintained.

Although it would be difficult to appreciate an effect of hypothermia alone on outcome, Eurotherm3235 demonstrated a lack of evidence supporting the benefit of therapeutic hypothermia in decreasing ICP and improving patient outcome 6 months after treatment. Interestingly, hypothermia resulted in a largely decreased need for pentobarbital-induced coma[14]. This may suggest that barbiturates provide similar or better metabolic suppression and neuroprotection as compared with hypothermia.

CONCLUSION

The overall goal of medical and surgical treatment for severe TBI is to prevent secondary injury by maintaining blood flow and oxygen delivery to the brain and minimizing swelling and pressure. The trials assessed in this review were not concerned with the challenge of isolating the effect of a single treatment, nor could they establish if successful treatment of intracranial hypertension improved outcomes. The collective effect of these investigations is to increase awareness of the lack of evidence supporting commonly used approaches for the management of patients with sTBI. It has become unclear how beneficial ICP monitoring, decompressive craniectomy, and therapeutic hypothermia are when compared to other standard treatment regimens. The unpredictable nature of the pathophysiology of traumatic brain injury demands guidelines for a pressure-focused approach to be more firmly established in order to effectively tailor treatment to the individual.

A recently completed study, BOOST 2 – Brain Tissue Oxygen Monitoring in Traumatic Brain Injury, is a multi-center randomized control phase 2 trial which uses a newly approved device to maintain continuous monitoring of the partial pressure of oxygen in brain tissue (pBrO2). 182 patients requiring ICP monitoring received both an ICP monitor and a pBrO2 monitor; patients in the control group had pBrO2 monitors masked by opaque tape in order to manage treatment based on ICP alone. Patients in the treatment group were managed based on results from both. Level of recovery was assessed 6 months after injury using GOS-E.[15] As the results of this trial are awaited, it can be noted that the treatment group incorporated two modalities to direct care for patients with sTBI. Although there is contention to the efficacy of some of these techniques individually, there may be a benefit in determining care based on evaluating and balancing more than one parameter. A multi-modal monitoring approach is a likely direction for future research into the management of patients with severe TBI.

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