

BRAIN INJURY

Head Injury Research: What Have We Learned?

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Learning Objectives: 1) To link the pathophysiology of traumatic brain injury to clinical research into the management of the problem, and 2) to examine some of the reasons for failure and success of such research.

Abstract

Clinical trials in head injury have been difficult to design. The heterogeneous nature of human traumatic brain injury, with a mixture of clots, contusions, diffuse axonal injury, and vasospasm in the same individual, means that the excellent therapeutic benefits demonstrated in animal models have not always been transferred to human conditions. Although the general management of traumatic brain injury, especially in the critical care environment, is well described, there is still a paucity of proven, evidence-based data for these treatment options. This article will attempt to review the reasons for the lack of success in translating some of the therapeutic modalities into clinical practice, as well as examine some of the current novel approaches to treatment.

The impact of traumatic brain injury (TBI) on health care systems is immense. There is now reasonable standardization in the basic prehospital and intensive care management of TBI.¹ Focus has therefore mainly shifted to pharmacologic interventions. Some therapeutic interventions have also been tested. Despite several modalities that have been tested over the last 20 years, the transfer of such therapy to the bedside has been disappointing. Indeed, trials that have shown great promise in animal models have failed to consistently show an improvement in human TBI. This has led researchers to believe that perhaps errors in human trial design and a failure to stratify patients into these trials could have had an impact on this failure of efficacy. However, despite these failures, there is little doubt that a much greater understanding of the pathophysiologic processes involved in TBI has emerged. This article will attempt to examine some of the significant trials and relate them to possible clinical usage.

Presented at the 17th Annual Trauma Anesthesia and Critical Care Symposium, Sydney, Australia, October 15–17, 2004.
 Dr. Guha has no conflicts of interest to disclose.

Outline of Pathophysiology

A brief understanding of the pathophysiology of TBI will clarify the targets identified by researchers. The primary injury leads to a cascade of events. A common CT scan finding is an intracranial hematoma, with or without contusions. Small vessels adjacent to the injury are damaged, and astrocyte swelling and cellular migration occurs. This forms the basis of the perilesional cerebral edema.² Consequent to this is a failure of supply of substrate such as glucose and oxygen to this area, leading to increased cellular damage. Astrocytes in the area swell up to add to the edema (cytotoxic cerebral edema). Other mechanisms in the edema formation include the kallikrein-kinin system.³ Thus, ischemic brain damage due to these mechanisms is common.⁴

In addition, substrate deprivation due to ischemia leads to sensitization of the glutamate-N-methyl D-aspartate (NMDA) receptor-calcium cascade.⁵ Glutamate acts as both a primary excitatory neurotransmitter and a potential neurotoxin within the mammalian brain. Excitatory amino acids, including glutamate and aspartate, are elevated significantly after TBI. Evidence indicates that hyperactivity of the glutamate system contributes to neuronal death. Free radical production, release of inflammatory mediators, and sensitization of the kallikrein-kinin system extend the neuronal injury subsequent to the primary insult.

Animal Research and Human Application

Human TBI in the clinical setting is a more heterogeneous injury with a combination of findings such as hematoma, contusion, diffuse axonal injury, and subarachnoid hemorrhage. This is rarely reflected in experimental models of animal injury. Researchers, therefore, may have been overambitious in trying to replicate the 10% or more improvement that is observed in several studies.⁶ A lack of power in several studies may have led to a failure to demonstrate efficacy.⁷ It is becoming clear that the patients who must be included in pharmacologic trials are those whose injuries most closely mimic the beneficial effects seen in a particular animal model.

Pharmacological Targets

Inflammatory Mediators. Corticosteroids. It has been known for some time that corticosteroids are beneficial in the reduction of peritumor brain edema. The Brain Trauma Foundation guidelines do not recommend the use of corticosteroids for treatment in cases of TBI.¹ However, the Cochrane review on the subject concluded that neither moderate benefits nor moderate harmful effects of steroids could be excluded.⁸

Following this, a worldwide trial was begun to examine the effects of Corticosteroid Randomization after Significant Head Injury (CRASH).⁹ The CRASH trial was a randomized, placebo-controlled, multicenter trial of a 48-hour corticosteroid infusion after significant head injury. The trial recruited 10,008 adult patients with head injury and a Glasgow Coma Scale (GCS) score of 14 or less within 8 hours

of injury. Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids. The cause of the rise in risk of death within 2 weeks was unclear.

Interleukin Receptor Antagonist. Inflammatory responses mediated by cytokines contribute to secondary damage in TBI. This response is now a major research focus. Increased expression of the cytokine interleukin-1 (IL-1) has been observed in rodents and in humans brain after injury, and IL-1 has been implicated in ischemic and excitotoxic brain damage in the rat.¹⁰ This effect can be diminished by administering the IL receptor antagonist (IL-RA). Evidence emerging from stroke trials reveals that the magnitude of the peripheral inflammatory response to stroke is related to the severity of acute ischemic stroke and clinical outcome.¹¹ This may have a bearing on the treatment of ischemic damage seen in TBI.

Vasospasm. Nimodipine. Vasospasm, and consequent ischemic damage, is integral to TBI. This is especially true in the presence of traumatic subarachnoid hemorrhage (SAH).¹² The use of nimodipine in the prevention of vasospasm-related ischemia following aneurysmal SAH is well established. This drug was therefore an obvious choice to be used in trials related to managing TBI that was accompanied by traumatic SAH. There have been such studies led by the Head Injury Trial Group (HIT I, II, and III).^{13,14} Although these trials tended to show a trend toward favorable outcome in TBI accompanied by traumatic SAH, unfortunately as many as 21% of patients' CTs reviewed later failed to identify an SAH component. The latest Cochrane review on the subject suggests that the effect of nimodipine in this subgroup of brain injury patients may have beneficial effect. However, nimodipine also appeared to be associated with an increased incidence of adverse effects.¹⁵ A new study, HIT IV, which will follow up the indications of benefit from nimodipine in patients with a traumatic subarachnoid hemorrhage, is underway in several parts of the world. The European Brain Injury Consortium was involved in the finalization of the protocol, and the final verdict is to come.

Free Radical Injury Modulators. Polyethylene Glycol-Conjugated Superoxide Dismutase. Formation of the oxygen radical superoxide anion is one of the final events of several metabolic pathways in the cascade that leads to delayed neuronal death after traumatic or ischemic brain injury.¹⁶ In the laboratory, scavenging of the superoxide anion with native superoxide dismutase (SOD) or polyethylene glycol (PEG)-conjugated SOD (PEG-SOD) had been shown to be beneficial in several types of traumatic and ischemic injury.¹⁷ The human trial failed to show any difference in Glasgow outcome score (GOS) or the disability rating score. However, patients who had received 10,000 U/kg compared with 20,000 U/kg of PEG-SOD showed a trend toward a better outcome.¹⁸ It must be pointed out, though, that intercenter variability in the routine treatment of TBI was not controlled⁶ and this may have contributed to the negative results.

Tirilazad. This is a novel noncorticosteroid aminosteroid that was shown to be effective in reducing TBI sequelae in rat models. This drug is an inhibitor of lipid membrane peroxidation and appears to function as an oxygen free radical scavenger.¹⁹ Despite initial good reports, further large, multicenter trials failed to show any significant improvements.²⁰ However, it has now become clear that there was large variation in controlling the basic prognostic parameters, e.g., hypotension and hypoxia.⁶ Although there was a better outcome observed in men, it was unclear whether

this was due to metabolic differences or to a large number of patients not being weighed.²¹

NMDA Receptor Antagonists. Glutamate/NMDA Receptor Modulators. Selfotel was the first glutamate antagonist that underwent Phase III clinical trial in studies of TBI.²² Despite some important neuroprotective evidence from animal experiments, all the research projects were shut down because of an increased mortality report from the concurrently running stroke trials.²³ This was a classic example of a drug company not staying the length required for trials because of initial adverse reports. There was no attempt made to study the concentration of the drug in the brain or the adequacy of the receptor blockade in the dosage the drug was administered.⁶

Similarly, the trial with Cerestat (aptiganel), another glutamate antagonist, was stopped by the sponsors after reports from their stroke trial showed that aptiganel was not efficacious in patients with acute ischemic stroke.²⁴ It would seem obvious that the pathophysiology in acute ischemic stroke does not exactly mirror that in TBI.

It has now become clear with animal research that NMDA receptors also help in neural regeneration.²⁵ Therefore, future trials must look at the timescale of administering the drug as well, so as to not interfere with the beneficial effects of such receptors.

New Directions. Dexamabinol. The activation of NMDA receptors in brain injury causing glutamate surges and cellular calcium ion influxes that ultimately lead to neuronal death led to interest in NMDA receptor antagonists. Dexamabinol is a cannabinoid and a noncompetitive NMDA receptor antagonist. There were encouraging results from initial studies regarding the limiting of edema formation and ischemic damage in stroke and TBI.²⁶⁻²⁸ A Phase II human trial has been conducted recently that included patients within 6 hours of TBI.²⁷ The aim of the study was to determine the safety of a single administration of escalating doses of dexamabinol, studied sequentially. The drug was not only shown to be safe, but there was a decrease in the mean time during which ICP (intracranial pressure) exceeded 25 mm Hg and the systolic blood pressure was less than 90 mm Hg.

The difference with dexamabinol, compared with earlier disappointing trials with NMDA antagonists such as selfotel, is perhaps because of its unique ability to not only block NMDA receptors, but also to act as an antioxidant and cytokine inhibitor. Dexamabinol inhibits TNF alpha and other inflammatory cytokines produced in culture and in animal models of inflammation. Dexamabinol also scavenges free radicals in vitro and in vivo. The Phase III trials with 861 U.S. and international patients with TBI has now concluded. The double-blind, randomized, placebo-controlled trial was conducted in 86 trauma centers in 15 counties. The manufacturers of Dexamabinol (Pharmos Corp., Iselin, New Jersey USA) stated in December 2004 that Dexamabinol did not demonstrate efficacy as measured by the primary clinical outcome endpoint, the Extended Glasgow Outcome Scale (GOSE). Not all secondary endpoints have been analyzed; however, no differences were observed in mortality or in analysis of subgroups in the trial.²⁹

Physiological Targets

Hypothermia. Hypothermia has been shown to be neuroprotective in many TBI models. Several mechanisms for this have been postulated, including decreased excitatory amino acids in the injured area,³⁰ augmenting antioxidant activity,³¹ and

reducing inflammatory markers.³² So far, randomized controlled trials of mild hypothermia (32–34°C) have provided conflicting results. Although Marion et al³³ were able to show a possible outcome benefit of mild hypothermia compared with normothermia in patients who had GCS scores of 5–7, the large U.S. multicenter NABIS:H1 (National Acute Brain Injury Study: Hypothermia) trial results failed to show any beneficial effect on outcome.³⁴ However, this study has been criticized on several counts: intercenter variability in treatment, delay in reaching target, and inconsistent fluid therapy. Because treatment benefit could be shown by subgroup analysis of patients who arrived at the study center with a low body temperature (<35.0°C), and in whom hypothermia was maintained, a second multicenter study with tighter protocols is in progress (NABIS:H2). The specific aim of NABIS:H2 is to determine if surface-induced moderate hypothermia (33°C for 48 hours) reached within 4 hours after severe brain injury improves outcome with low toxicity in patients aged 16–45 and with a low admission temperature (<35.0°C).³⁵

Cerebral Perfusion Pressure-ICP Trials

It has been recommended for some time that, after severe TBI, the target cerebral perfusion pressure (CPP) should be 70 mm Hg or higher.³⁶ However, recent recommendations from the Brain Trauma Foundation suggest that, in the absence of cerebral ischemia, aggressive management of CPP exceeding 70 mm Hg is not recommended.³⁷ A minimum CPP of 60 mm Hg should be maintained. This is largely derived from the work of Robertson and colleagues,³⁸ where patients were randomized into ICP (CPP kept above 50 mm Hg) and CPP (CPP kept above 70 mm Hg) management groups. There was no significant difference in overall outcome in the two groups, but the incidence of ARDS was higher in the CPP group, which offset any CPP-related benefit.

There is little doubt that the time has come to individualize a patient's cerebral physiological responses, and not treat everyone by using the same protocol. There is yet no single, ideal monitoring tool for the brain, but a combination of ICP, jugular venous saturation, intermittent cerebral perfusion imaging, and the use of cerebral tissue microdialysis could be useful. The debate will continue of justifying this expense when robust outcome studies are awaited.

Conclusion

Animal models of head injury have contributed significantly to our understanding of TBI, and will continue to form the template for testing physiological and pharmacologic treatment. It has become clear after decades of research that some evidence must first be gathered that the mechanisms governing animal models of injury apply to humans as well. Pharmacologic agents have to undergo robust Phase I and II trials with evidence of effective drug concentration in the CNS. Large trials are required, but with tightly controlled inclusion, exclusion, and treatment criteria to prevent erroneous conclusions being drawn. The timing of application of such therapy must be considered. It is extremely important to standardize the general intensive care management of these patients to avoid intercenter variability. Additionally, larger trials may enable us to identify certain subgroups in the population that may significantly benefit from the therapeutic interventions.

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Serum Markers of Severe Traumatic Brain Injury: Are They Useful?

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Learning Objective: To present new, additional means of assessing, monitoring, and managing ongoing brain damage in order to limit the development of secondary brain damage in intensive care patients suffering from severe traumatic brain injury.

Abstract

S100B, neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP) are the most well-known and most-used serum markers at present. NSE and S100B may have some utility if properly interpreted and tracked, but have significant limitations in terms of single measurements and lack of specificity. GFAP appears to be much more helpful, with much higher specificity. Nevertheless, GFAP needs to be validated in larger studies, and correlated with outcomes. It is conceivable that future intensivists will be using a panel of markers to assess primary brain injury, detect ongoing secondary brain injury, and possibly even assess the benefits of neuroprotective drugs.

Background

Before attempting to answer whether or not serum markers are "useful," let us first briefly consider the pathophysiology of severe traumatic brain injury (TBI) as we see it in the trauma intensive care unit. One of the main problems is the development of secondary brain damage triggered by both primary trauma and increased intracranial pressure, decreased mean arterial pressure, and decreased cerebral perfusion pressure.¹ One of the main difficulties the intensivist is faced with is monitoring and managing patients to provide continuous effective critical care and to limit the development of secondary brain damage. Obviously, the more severely injured the patient is, the more difficult monitoring and management may become; i.e., although patients with severe isolated TBI are sometimes difficult to manage, patients with additional multiple trauma can pose an even greater challenge. In recent years, improved intracranial pressure monitoring and modern neuroimaging techniques such as computed tomography and magnetic resonance imaging have contributed greatly to the assessment and care of patients with TBI.² Nevertheless, for all their accuracy, both techniques are expensive, and not always available. Above all, they are associated with stress for patients with TBI (transport to the CT and monitoring en route) and thus cannot be considered suitable for frequent follow-ups. Thus, assessment, monitoring, and management of TBI remain difficult for the intensivist and often stressful for the patient. A serum test measuring one or more markers to determine the status quo of brain damage would no doubt be welcome in the setting of severe TBI. Such markers would be useful indeed in guiding critical care and evaluating the prognosis of patients with severe TBI.

Similar to tests for damage to other organs (i.e., troponin for damage to the heart), a test for damage to the brain might well be based on the measurement of one (or more) serum marker(s). Ideally, markers of brain damage should be measurable quickly and simply, and should be measurable in serum, since serum is more readily available than cerebrospinal fluid.³ Above all, however, ideal markers of brain damage should be both highly brain-specific and sensitive.⁴

Since the early 1980s, there has been an increasing amount of research on markers of brain damage. Easily detectable substances derived from neurons and glia were measured by commercially available assays and studied as

Presented at the 17th Annual Trauma Anesthesia and Critical Care Symposium, Sydney, Australia, October 15-17, 2004.
Dr. Pelinka has no conflicts of interest to disclose.