

Head injury research: What have we learnt?

To link the pathophysiology of traumatic brain injury (TBI) to clinical research into the management of the problem, and to examine some of the reasons for failure and success of such research.

Clinical trials in head injury have been difficult to design. The heterogenous nature of human TBI, 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 TBI, 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.

Introduction

The impact of traumatic brain injury (TBI) on health care systems is immense. There is now reasonable standardisation in the basic pre-hospital and intensive care management of TBI. Focus has therefore mainly shifted to pharmacological interventions. Some therapeutic interventions have also been tested. Despite several modalities which have been trialled over the last twenty years the transfer of such therapy to the bedside has been disappointing. Indeed, trials that have showed 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 pathophysiological processes involved in TBI has emerged. This paper will attempt to examine some of the significant trials and relate that to possible clinical usage.

Outline of pathophysiology

A brief understanding of the pathophysiology will clarify the targets identified by researchers.

The primary injury leads to a cascade of events. A common CT scan finding is an intracranial haematoma, 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 peri-lesional cerebral oedema (1). 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 oedema (cytotoxic cerebral oedema). Other mechanisms in the oedema formation include the kallikrein-kinin system. (2). Thus, ischaemic brain damage due to these mechanisms is common (3).

In addition, substrate deprivation due to ischaemia leads to sensitisation of the glutamate-NMDA receptor-calcium cascade (4). Glutamate acts both as a primary excitatory neurotransmitter and a potential neurotoxin within the mammalian brain. Excitatory amino acids (EAA), 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 sensitisation of the kallikrein-kinin system extends 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 haematoma, contusion, diffuse axonal injury, subarachnoid haemorrhage, etc. This is rarely reflected in experimental models of animal injury. Therefore researchers may have been overambitious in trying to replicate the 10% or more improvement that are observed in several studies (5). Therefore, a lack of power in several studies may have led to a failure to demonstrate efficacy (6). It is becoming clear that patients must be included into pharmacologic trials whose injuries mostly mimic 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 peri-tumour brain oedema. The Brain Trauma Foundation (BTF) (7) guidelines do not recommend the use of corticosteroids in TBI. However, the Cochrane review on the subject (8) concluded that neither moderate benefits nor moderate harmful effects of steroids could be excluded. When all previous trials of steroids in head injury were combined, the risk of death in the corticosteroid

treated group appears to be about 2% lower than in the control group.

Following on from this, a worldwide trial began to examine the effects of Corticosteroid Randomisation After Significant Head Injury (CRASH). (9). The CRASH Trial is a randomized, placebo-controlled, multicentre trial of a 48-hour corticosteroid infusion after significant head injury and is now the largest head injury trial ever conducted. By spring 2004, 8,500 patients had been randomised.

ILRA

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

Vasospasm

NIMODIPINE

Vasospasm, and consequent ischaemic damage is integral to TBI. This is especially true in the presence of traumatic subarachnoid haemorrhage (SAH) (12).

The use of nimodipine is well established in the prevention of vasospasm related ischaemia following aneurysmal SAH. Interest was therefore going to be obvious in trialling this drug in managing TBI accompanied by traumatic SAH. There have been studies led by the Head Injury Trial Group (HIT I, II and III). Although these trials tended to show a trend towards favourable outcome in TBI accompanied by traumatic SAH, unfortunately as many as 21% of patient's CTs reviewed later failed to identify an SAH component. The latest Cochrane review on the subject (13) suggests that the effect of nimodipine in this subgroup of brain injury patients may be beneficial effect. A new study, HIT-IV to follow up the indications of benefit from nimodipine in patients with a traumatic subarachnoid haemorrhage, is underway in several parts of the world. The European Brain Injury Consortium was involved in the finalisation of the protocol, and the final verdict is awaited.

Free radical injury modulators

PEG-SOD

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 (14). 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. (15). The human trial failed to show any difference in Glasgow Outcome score (GOS) or Disability Rating Score (DRS). However, patients who had received 10,000 U/kg compared to 20,000 U/kg trended towards a better outcome (16) However, inter-centre variability in routine treatment of TBI was not controlled (5) and may have contributed to the negative results.

TIRILAZAD

This is a novel non-corticosteroid aminosteroid that was shown to be effective in reducing TBI sequelae in rat models. They are inhibitors of lipid membrane peroxidation and appear to function as oxygen free radical scavengers (17). Despite initial good reports, further large, multicentre trials failed to show any significant improvements (18). However, it has now become clear that there were large variation in controlling basic prognostic parameters, e.g. hypotension and hypoxia (5). Though there was a better outcome observed in men, it was unclear whether this was due to metabolic differences or to large number of patients not being weighed! (19).

NMDA receptor antagonists

GLUTAMATE / NMDA RECEPTOR MODULATORS

Selfotel was the first glutamate antagonist that underwent Phase III clinical trial in TBI (20). Despite some important neuroprotective evidence from animal experiments, due to an increased mortality report from the concurrently running stroke trials (21), all the research projects were shut down.

This was a classic example of a drug company not staying the length required after initial adverse reports. There was no attempt made to study concentration of the drug in the brain or the adequacy of receptor blockade in the dosage the drug was administered (5)

Similarly, the trial with Cerestat (aptiganel), another glutamate antagonist, was stopped by the sponsors after reports from their stroke trial (22) showed that aptiganel was not efficacious in patients with acute ischemic stroke. It would seem obvious that the pathophysiology is acute ischaemic stroke does not exactly mirror that in TBI.

It has also now become clear with animal research that NMDA receptors also help in neural regeneration (23). 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

DEXANABINOL

The activation of N-methyl D-aspartate (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. Dexanabinol is a cannabinoid and a non-competitive NMDA receptor antagonist. Initial

studies were encouraging in stroke and TBI in limiting oedema formation and ischaemic damage (24, 25, 26). A Phase II human trial has been conducted recently which included TBI patients within 6 hr of injury (25). The aim of the study was to determine the safety of a single administration of escalating doses of dexanabinol, studied sequentially. It was not only shown to be safe, but the mean time during which ICP exceeded 25 mmHg and systolic BP was less than 90 mmHg was decreased.

The difference with dexanabinol, compared to earlier disappointing trials with NMDA antagonists such as selfotel is perhaps due to its unique ability to not only block NMDA receptors, but act additionally as an antioxidant and cytokine inhibitor. Dexanabinol inhibits TNF alpha and other inflammatory cytokines produced in culture and in animal models of inflammation. Dexanabinol also scavenges free radicals in vitro and in vivo.

It is currently in Phase III trials. By mid-March 2004, the Company completed enrolment of 861 U.S. and international TBI patients and results of the trial are expected by the end of 2004. Dexanabinol is unique among neuroprotective agents because it combines in one molecule three mechanisms of action that suppress toxic and inflammatory cascades induced by TBI. In addition, the tight inclusion criteria, e.g. presence of "severe" TBI, administration within six hours of injury (the therapeutic window determined in preclinical experiments) following well carried out pre-clinical trials may well mean that a pharmacological agent that is clinically useful in TBI is on the horizon (27).

Physiological targets

HYPOTHERMIA

Hypothermia has been shown to be neuroprotective in many TBI models. Several mechanisms for this has been postulated, including decreased excitatory amino acids in the injured area (28), augmenting antioxidant activity (29) and reducing inflammatory markers (30). So far, randomized controlled trials of mild hypothermia (32-34°C) have provided conflicting results. Although Marion (31) was able to show a possible outcome benefit of mild hypothermia compared to normothermia in patients who had GCS scores of 5-7, the large US, multicentre, NABIS H1 (National Acute Brain Injury Study: Hypothermia) trial results failed to show any beneficial effect on outcome (32). However, this study has been criticised on several counts: inter-centre variability in treatment, delay in reaching target, and inconsistent fluid therapy. As treatment benefit could be shown by subgroup analysis in patients who arrived at the study center with a low body temperature ($\leq 35.0^{\circ}\text{C}$), and in whom hypothermia was maintained, a second multicentre 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 four hours after severe brain injury improves outcome with low toxicity in patients age 16 – 45 years and a low admission temperature ($< 35.0^{\circ}\text{C}$) (33).

CPP-ICP TRIALS

It has been recommended for some time that after severe TBI, the target cerebral perfusion pressure (CPP) should be 70 mmHg or above (34). However, recent recommendations from the BTF suggest that in the absence of cerebral ischaemia, aggressive management of CPP > 70 mmHg is not recommended (35). A minimum CPP of 60 mmHg should be maintained. This is largely derived from the work of Robertson and others (36), where patients were randomised into 'ICP' (CPP kept above 50 mmHg) and a 'CPP' (CPP kept above 70 mmHg) 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 individualise a patient's cerebral physiological responses, and not treat everybody using the same blanket protocol. There is no single, ideal monitoring tool for the brain yet, but a combination of ICP, jugular venous saturation, intermittent cerebral perfusion imaging, and the use of cerebral tissue microdialysis could be useful. The debate of justifying this expense when robust outcome studies are awaited will continue.

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 pharmacological 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. Pharmacological 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 standardise the general intensive care management of these patients to avoid inter-centre 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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