Promising strategies to minimize secondary brain injury after head trauma

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**Objective:** To review novel therapeutic approaches in the treatment of severe traumatic brain injury.

**Design:** Eighty-three studies were reviewed specific to the treatment of traumatic brain injury, in either experimental models or in patients.

**Conclusion:** Four therapeutic strategies appear to be the most promising approaches currently in clinical trials for severe traumatic brain injury: a) the novel pharmacologic agent dexanabinol; b) hypertonic saline; c) mild hypothermia; and d) decompressive craniectomy. Each of these therapies share the common feature of targeting multiple mechanisms, suggesting this may be an important factor to the development of a successful approach to severe traumatic brain injury.

**Key Words:** traumatic brain injury; hypothermia; hypertonic saline; craniectomy; therapy; cerebral resuscitation; cerebral edema; dexanabinol

Traumatic brain injury (TBI) is a major health problem, with annual incidence rates estimated as 500,000 cases in the United States alone (1). However, targeted therapies for TBI are lacking and treatment remains largely supportive. Clinical trials of therapies directed toward targeting pathophysiologic derangements occurring in TBI have been difficult to design and conduct because of the multiple factors affecting the outcome from TBI. Success of the clinical trials in TBI has been suggested to depend on selection of a potent inhibitor of an important deleterious mechanism that occurs in TBI, confirmation of adequate drug delivery to the brain, standardization of clinical management within and across centers, selection of measurable, standard, and relevant outcome parameters, adequate powering of the study, and targeting the subpopulation of the patients most likely to benefit from therapy (1, 2).

However, multiple mechanisms lead to secondary damage after TBI. Four key mechanistic categories are those associated with the following: a) ischemia, excitotoxicity, and energy failure; b) neuronal death cascades; c) cerebral swelling; and d) inflammation. Cerebral blood flow is reduced early after severe TBI and might represent a therapeutic target (3, 4). Loss of endogenous vasodilators (such as nitric oxide) (5) and elaboration of vasoconstrictors (such as endothelin-1) (6) could be involved in producing early posttraumatic hypoperfusion. Ventricular cerebrospinal fluid glutamate concentrations have been shown to increase after TBI in humans to levels sufficient to produce excitotoxic neuronal death in culture (7). Glutamate exposure produces neuronal injury first by sodium-dependent neuronal swelling (8), then by calcium-dependent degeneration, with resultant oxidative and nitrosative stress. These effects are mediated through both ionophore-linked receptors, labeled according to specific agonists (N-methyl-D-aspartate [NMDA], kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) and receptors linked to secondary messenger systems. Brain swelling from a number of causes is important in severe TBI (9). Both osmolar swelling in contusions and astrocyte swelling as a result of excitotoxicity appear to be important. Brain swelling can lead to secondary ischemia and/or herniation, with devastating consequences. A variety of neurotransmitter systems are important, depending on the local circuitry. Although a portion of neuronal death after TBI occurs immediately after the initial insult, some neurons die in a delayed fashion by programmed cell death (10). Targeting specific upstream regulators of programmed cell death cascade or using other therapies with broad effect, such as hypothermia, may reduce neuronal death after TBI. Finally, inflammation has been shown to occur after experimental (11) and clinical TBI (12). Inflammation has acute detrimental and subacute/chronic beneficial aspects in recovery and regeneration (13). Clearly, mechanisms involved in the evolution of damage after severe TBI are multifactorial, cybernetic, and complex.

A number of specific therapeutic agents have been tested for their ability to ameliorate secondary damage after TBI. Many of these agents have focused on a single mechanism. Unfortunately, no single “magic bullet” has been developed for the treatment of TBI. In this review, we discuss four promising therapeutic approaches that are in clinical trials: dexanabinol, hypertonic saline, mild hypothermia, and decompressive craniectomy. Each of these agents targets multiple mechanisms (Fig. 1).

**Dexanabinol**

Dexanabinol is a synthetic, nonpsychoactive cannabinoid (14). It is a noncompetitive NMDA receptor antagonist (15). Dexanabinol also has been shown to...
Preclinical studies have shown the efficacy of dexanabinol in experimental TBI and stroke with a therapeutic window of 6 hrs (18–20). A phase I study demonstrated that dexanabinol was safe at doses up to and including 200 mg (21).

One hundred one adults who sustained TBI, were admitted to the hospital within 6 hrs, had a Glasgow coma scale (GCS) score of 4–8, and had computed tomographic findings of category 2 or above were enrolled in a phase II clinical trial (22). The patients were randomized to receive either placebo or one of the following three doses of dexanabinol: 48 mg, 150 mg, or 200 mg given as a single dose (1, 23). In this trial, only patients requiring intracranial pressure (ICP) monitoring were enrolled in the study because of the proposed beneficial effects of dexanabinol on breakdown of the blood-brain barrier and edema formation (16). Most of the patients were in the 20- to 40-yr-old age range, 80% were males, and 70% had been involved in a motor vehicle accident. Dexanabinol was shown to be safe and well tolerated in the dose range tested, and there were no significant differences in adverse events between the patients who received placebo and those who received the drug. A single administration of the drug decreased the mean time during which ICP exceeded 25 mm Hg and systolic blood pressure was <90 mm Hg. Treatment did not significantly effect the 6-month Glasgow Outcome Score, although this study was not powered to show efficacy.

Dexanabinol is in phase III trials for TBI. The observed reduction in both intracranial hypertension and systemic hypotension, along with the antieuxcitotoxic, antioxidant, and anti-inflammatory properties of dexanabinol, is promising for the treatment of TBI. Although, previous studies of more specific NMDA antagonists, such as selfotel (24), or antioxidants, such as polyethylene glycol-conjugated superoxide dismutase and tirilazad (25, 26), failed to demonstrate efficacy, it is possible that a combination of potentially therapeutic effects would be more effective than an agent targeting a single mechanism. Excitatory amino acid concentrations are maximal early after injury in animals (27). Similar findings have been shown in humans as well (28). This finding may explain, at least in part, why human trials targeting excitotoxicity have failed. For dexanabinol, the best treatment outcomes in rats have resulted when treatment was started within 1 hour of injury and a second injection was given after 6 hrs (1). The results of the phase III trials of this agent could serve as a test case for drugs targeting multiple mechanisms in TBI, so called “dirty drugs.”

**Hypertonic Saline**

Based on the hypothesis that tissue osmolar load may be more important than increases in cerebral blood volume and blood-brain barrier permeability in the development of cerebral swelling after TBI, osmolar treatment with hypertonic saline seems logical. Apart from its osmotic properties, hypertonic saline has hemodynamic, vasoregulatory, and immunomodulatory effects after TBI (29). Hypertonic saline improves and maintains mean arterial pressure in patients after trauma (30, 31). Changes in circulating hormone levels, as well as plasma volume expansion, have been implicated as being important causes of these hemodynamic effects (32). Both hypoperfusion owing to vasospasm and hyperemia have been described after TBI (4, 33). Postulated mechanisms explaining the vasoregulatory properties of hypertonic saline include the following (34, 35): plasma volume expansion leading to increased vessel diameter, decreased endothelial cell edema, and decreased vascular resistance secondary to the release of nitric oxide. Experimental models of TBI also suggest that hypertonic saline inhibits posttraumatic activation of leukocytes (36). However, it is likely, particularly in the setting of contusion, that the key effect of hypertonic saline is reduction of osmolar swelling (37). Similarly, numerous experimental studies have shown that hypertonic saline reduces cerebral water content through dehydration of uninjured brain regions (38).

Clinical trials of hypertonic saline generally have been limited to patients who failed conventional management. Worthley et al. (39) reintroduced hypertonic saline by reporting two TBI patients with intractable ICP, who were successfully treated with 20 mL of 29.2% hypertonic saline. This finding was followed by favorable reports in models of TBI combined with hypotension (40). Fisher et al. (41) reported that a single bolus of hypertonic saline reduced ICP in 18 brain-injured children. However, a randomized, controlled trial of hypertonic saline vs. lactated Ringer’s solution in adults with severe TBI showed no treatment effect (42). Subsequent reports of hypertonic

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**Figure 1.** Dexanabinol, hypertonic saline, mild hypothermia, and decompressive craniectomy represent four therapies currently in clinical trials that target multiple mechanisms (as indicated by the + signs), including ischemia, neurotoxic cascades, cerebral swelling, and/or inflammation. BBB, blood-brain barrier; CBV, central blood volume; ICP, intracranial pressure.
saline use in adults with TBI yielded conflicting findings. Qureshi et al. (43) reported on retrospective data that suggested that increasing serum sodium to levels between 145 and 155 mEq/L with a continuous infusion of 3% hypertonic saline reduced ICP. Subsequently, the same group was unable to show a beneficial effect of hypertonic saline in 36 adult patients with severe TBI (44). In contrast, studies in children suggest a benefit from hypertonic saline in TBI. An open-label, randomized, prospective study of 1.7% hypertonic saline vs. Ringer’s lactate as a maintenance fluid for the first 72 hrs after admission in 32 children with severe TBI showed an inverse relationship between serum sodium and ICP (45). Peterson et al. (46) reported a retrospective study of 68 children with severe TBI treated with a continuous infusion of 3% hypertonic saline. Hypertonic saline controlled ICP in most cases. A prospective evaluation of a sliding scale of 3% saline infusion was associated with favorable control of ICP by the same group (47). In this study, a prospective control group receiving standard therapy was lacking, cerebrospinal fluid drainage was used very infrequently, and the serum sodium concentration required to achieve ICP control was high. Nevertheless, outcomes were quite favorable and hypertonic saline appeared to be safe, even when serum osmolality was higher than previously thought to be acceptable with mannitol therapy.

The primary theoretical concerns associated with the use of hypertonic saline include the development of central pontine myelinolysis (CPM), rapid shrinking of the brain associated with mechanical tearing of bridging vessels leading to subarachnoid hemorrhage, renal failure, and rebound intracranial hypertension. CPM is characterized by demyelination, primarily of the pons, and clinically by the onset of lethargy and quadriplegesis (48). CPM has been reported with rapid correction of chronic hyponatremia to serum sodium levels of >132 mEq/L (48). CPM has not been reported in human trials of hypertonic saline in TBI. Peterson et al. (46) performed magnetic resonance imaging evaluations in 11 of 68 patients in their study, and none had evidence of CPM. However, rats with normoglycemic serum sodium that were subjected to an increase in serum sodium of 39 ± 8 mEq/L showed severe demyelinating lesions (49). Subarachnoid hemorrhage caused by hypertonic saline administration has been reported, but only when the serum sodium concentration increased from 149 to 206 mEq/L within 1 hr in normal kittens (50). Although kidney failure is a primary concern with the use of hypotonic therapies, maintaining euvoolemic during the administration of hypertonic saline for the treatment of TBI appears to prevent renal complications. When compared with Ringer’s lactate solution, hypertonic saline used for the resuscitation of burn patients has been associated with a four-fold increase in renal failure (51). However, renal failure has not been observed in animal models (52) and humans with TBI (46). Rebound intracranial hypertension has been described with the use of hypertonic saline for ICP control with bolus therapy or after cessation of continuous infusion (46, 53). Patients may require a progressive increase in the infusion rate of hypertonic saline to control ICP (46). It is unclear whether this is truly a rebound effect or natural evolution of the patient’s brain injury.

Currently hypertonic saline represents an acceptable tool to treat intracranial hypertension in pediatric TBI, either as a first- or second-tier therapy. In adults, however, its use is only supported for the treatment of refractory intracranial hypertension. Multicenter clinical trials are needed to explore the optimal use of hypertonic saline and to compare this agent with mannitol therapy.

Mild Hypothermia

Mild hypothermia (32–34°C) has been shown to be neuroprotective in a variety of animal species and models of injury (54). In mechanistic studies, mild hypothermia decreases excitatory amino acid levels in the peritrauma region (55) as well as in cerebrospinal fluid of TBI patients (12). Mild hypothermia has been shown to decrease endogenous antioxidant consumption and lipid peroxidation after experimental brain injury (56) and to preserve cerebrospinal fluid antioxidant reserves after TBI in children (57). Mild hypothermia also has anti-inflammatory effects as demonstrated by decreased cerebrospinal fluid interleukin-1β (12), plasma interleukin-6, and prostanoid levels (58) in patients treated with hypothermia vs. normothermia.

Three randomized control trials of mild hypothermia (32–33°C) were conducted in adults with conflicting results. Clifton et al. (59) reported a feasibility study in 46 patients with GCS scores of 4–7 who were randomized within 6 hrs of injury to hypothermia or normothermia treatment for 48 hrs. Although hypothermia was found to be safe, no beneficial effect of hypothermia was seen on functional outcome, possibly because of the small sample size. A second trial by Marion et al. (12) reported on 87 patients with GCS scores of 3–7 who were randomized within 6–24 hrs to receive mild hypothermia or normothermia; an improvement was shown in the Glasgow Outcome Scale scores of patients with GCS scores of 5–7, but not in patients with GCS scores of 3–4. The third trial, which included 11 U.S. centers, enrolled 392 patients with GCS scores of 3–7 who were randomized to mild hypothermia vs. normothermia for 48 hrs; this study failed to show a beneficial effect of treatment on outcome (60). In addition, there were statistically significant increases in complications (such as bleeding, sepsis, and pneumonia) in the hypothermia group, particularly in patients older than 45 yrs of age. This study has been criticized for potentially missing the treatment window for therapeutic hypothermia, because the target temperature was not achieved until 8.4 ± 3 hrs after injury (61). There were also intercenter differences in the outcomes of patients (62). Furthermore, patients treated with mild hypothermia received significantly more fluids, with a mean fluid balance of 3 L positive within 96 hrs compared with 2.6 L in normothermic patients (63). Multicentered, randomized control trials of mild hypothermia in infants and children with severe TBI are ongoing in Canada and the United States, and another trial in adults is likely. Finally, the two recent positive clinical trials of mild hypothermia after cardiac arrest in adults also support the potential value of this therapy in central nervous system injury (64, 65).

Decompressive Craniectomy

Surgical decompression to expand the intracranial space and to reduce ICP has been recognized since the beginning of the 19th century (66). Recently, there has been increasing interest in this modality for the treatment of refractory intracranial hypertension. Both experimental and clinical studies showed the efficacy of decompressive craniectomy in reducing ICP (67–71). However, there have been reports of exacerbation of cerebral edema...
Successful therapy for severe traumatic brain injury may require favorable effects on multiple deleterious cascades rather than specific targeting of a single pathophysiologic derangement.

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REFERENCES


70. Hase U, Reulen HJ, Meinig G, et al: The...


