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Severe traumatic brain injury: Controversies in management

BY JAMES S. HUTCHISON, MD

Head injury is the most common cause of mortality and acquired disability in children, adolescents, and young adults,^{1,2} accounting for 33 new cases of disability per 100,000 people per year in the United States.³ Mortality rates are declining with improvements in pre-hospital stabilization and transport, as well as in emergency room, intensive care, and operating room management. The principles of management recommend a multidisciplinary approach to monitor and prevent secondary injury. Evidence-based approaches, including management guidelines for initial stabilization, supportive care, and the monitoring and control of intracranial pressure,⁴ increase the level of vigilance and attention to detail in management that is necessary to decrease secondary injury and potentially improve outcome.

When reviewing the evidence supporting specific therapies for management of severe head injury, there are many areas of controversy. A recent meta-analysis found a paucity of randomized, controlled trials to support many of the common therapies used in managing these injuries.⁵ Controversy over management arises when there are areas of uncertainty in the literature. In this issue of *Critical Care Rounds*, I will discuss several therapies that are controversial in the management of severe traumatic brain injury, including cerebral perfusion pressure-directed therapy, corticosteroids, hypertonic saline, hypothermia, and decompressive craniectomy. My aim is to provide some clarity to help the practitioner make management decisions.

Guidelines for management

Evidence-based guidelines for management of severe traumatic brain injury (defined as a Glasgow Coma Scale [GCS] of ≤ 8) were published by the Brain Trauma Foundation and The American Association of Neurological Surgeons (AANS) in 1995⁶ and again in 2000.⁴ European and Japanese guidelines did not include critical reviews of the literature.^{7,8}

In the AANS guidelines, recommended therapies include initial oxygenation, intubation and ventilation, fluid resuscitation and sedation \pm short-acting neuromuscular blockade.⁹ Particular emphasis is placed on the prevention and treatment of hypotension¹⁰ that leads to cerebral ischemia and is known to be associated with increased mortality and a worse neurological outcome in survivors of traumatic brain injury.¹¹⁻¹³ Hyperventilation is reserved for herniation or neurological deterioration not attributable to extracranial causes.⁹ Prolonged hyperventilation has been shown to worsen neurological



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outcome following traumatic brain injury.¹⁴ If hyperventilation is used in the initial resuscitation, other therapies to reduce intracranial hypertension are recommended, such as mannitol, but only with adequate volume resuscitation.⁹

Further management practices recommended in the AANS guidelines include CT scan and the monitoring and control of intracranial pressure to <20-25 mm Hg.⁴ Intracranial hypertension can signal an acute neurosurgical emergency and is associated with a higher mortality and worse neurological outcome in a patient with a severe traumatic brain injury. Therefore, intracranial pressure should be monitored and controlled. Recommended therapies to reduce intracranial hypertension include mannitol (again with adequate volume resuscitation) and mild hyperventilation. Second tier therapies are recommended for intracranial hypertension refractory to conventional therapies, but are associated with significant complications. These therapies include hyperventilation to PaCO₂ <30 mm Hg, barbiturates, decompressive craniectomy, and hypertensive therapy (Table 1).⁴

The AANS guidelines recommend that cerebral perfusion pressure be monitored and controlled at >70 mm Hg as a treatment option in adults with severe traumatic brain injury.¹⁵ The next section outlines the controversy associated with cerebral perfusion pressure-directed therapy. Therapies not recommended in the AANS Guidelines that are currently the subject of intense investigation are corticosteroids, hypertonic saline, and hypothermia.

Therapies in the management of severe traumatic brain injury

Controlling cerebral perfusion pressure

Cerebral perfusion pressure is mean arterial pressure minus intracranial pressure. The objective of monitoring and controlling cerebral perfusion pressure above a certain threshold is to prevent low cerebral blood flow and cerebral ischemia. Robertson et al carried out the only randomized controlled trial of cerebral perfusion pressure-directed therapy.¹⁶ In this trial, 189 adults with severe traumatic brain injury were randomized to either a cerebral blood flow/cerebral perfusion pressure-driven protocol or an intracranial pressure-driven protocol. The cerebral blood flow/cerebral perfusion pressure group had a lower incidence of jugular venous desaturation (30% vs 50.6%, $P=0.006$). However, there was no statistically significant difference in favourable neurological outcome (39.8% for cerebral blood flow/cerebral perfusion pressure vs 49.3% for intracranial pressure, $P=0.49$). Of greater

Table 1: Methods to reduce intracranial hypertension

Initial therapy

- Elevate head of bed
- Keep head in midline position
- Sedation
- Analgesics
- Mannitol
- Neuromuscular blockers
- Mild hyperventilation

Secondary therapy

- Barbiturates
- Hypertensive therapy
- Moderate hyperventilation (PaCO₂ < 30 mmHg)
- Decompressive craniectomy

concern was the relatively high incidence of respiratory distress syndrome in the cerebral blood flow/cerebral perfusion pressure group (15% vs 3.3%, $P=0.007$).

In a completely different approach to the management of cerebral perfusion based on a microvascular model, clinicians and scientists in Lund, Sweden, proposed lowering arteriolar hydrostatic pressure, elevating intravascular oncotic pressure, and lowering venous hydrostatic pressure to prevent cerebral edema following traumatic brain injury.¹⁷ This is done using β_1 -antagonists and vasodilators, while normalizing blood volume with red blood cell and albumin transfusions. Cerebral perfusion pressure is maintained >50 mm Hg in adults and >40 mm Hg in children. Vasopressors are used transiently in specific cases for reversal of hypotension. The “Lund therapy” is complex and essentially represents a non-evidence-based guideline for therapy.¹⁷ Three case series have been reported using the “Lund therapy” in a total of 123 patients with severe traumatic brain injury.¹⁸ Of the 123 patients, approximately 70% had a favourable outcome (Glasgow outcome scale of good recovery or moderate disability) and mortality was approximately 10%.

The cerebral perfusion pressure approach and the “Lund therapy” have one principal in common. Normovolemia is maintained and hypotension is meticulously monitored, prevented, and treated. Hypotension (systolic blood pressure ≤ 90 mm Hg) is a common occurrence during transport and in the emergency room, the CT scanner, the intensive care unit, and the operating room; it doubles the mortality of patients with traumatic brain injury.^{11,19}

The mechanism of hypotension-induced secondary brain injury following trauma is ischemia. Recently, the

mechanism of hypoxic-ischemic brain injury following traumatic brain injury was explored in a mouse model (unpublished data). Hypoxic-ischemic insult led to an exponential increase in the rate of genetically programmed cell death or apoptosis following trauma that was both dose- and time-dependant. There was a 15-fold increase in the number of apoptotic cells adjacent to contusions following trauma with the addition of a hypoxic-ischemic insult, compared to animals with trauma alone (no hypoxia-ischemia). The same hypoxic-ischemic insult did not induce apoptosis in normal mouse brain (no trauma). Our conclusion is that brain cells are selectively vulnerable to apoptosis induced by secondary brain insults following trauma. Secondary insults from hypoxia and ischemia should be meticulously monitored, prevented, and treated rapidly following traumatic brain injury.

Corticosteroids

Neuroinflammation occurs following traumatic brain injury and may contribute to apoptosis.²⁰ Inflammation also leads to a breakdown in the blood-brain barrier and cerebral edema.²¹ Anti-inflammatory therapies, including steroids, decrease edema and are effective in traumatic spinal cord injury,^{22,23} but it is not known if they are beneficial in traumatic brain injury. A recent meta-analysis of 14 randomized, controlled trials of corticosteroids in traumatic brain injury showed no benefit, but the confidence intervals crossed both harm and benefit, therefore justifying a large, multicentre, randomized controlled trial.²⁴ The Corticosteroid Randomization After Significant Head injury (CRASH) study is in progress. It is powered to detect a 2.6% difference in mortality and has enrolled approximately 2500 patients to date. For more information or if you are interested in joining the study see the website: <http://www.crash.lshtm.ac.uk>.

Hypertonic saline

Hypertonic saline has been used for volume resuscitation in patients with hemorrhagic shock following trauma and for lowering intracranial pressure. Three randomized controlled trials of hypertonic saline for patients with traumatic brain injury (2 pediatric and 1 adult) have been published.

- A blinded, cross-over study of the effect of a 2-hour infusion of hypertonic saline on intracranial pressure in 18 children following traumatic brain injury reported reduced intracranial pressure with hypertonic saline.²⁵

- An open, randomized, controlled trial of a 3-day infusion of hypertonic saline versus Ringer's lactate in

35 consecutive children with traumatic brain injury found shortened ICU length of stay and fewer interventions to reduce intracranial pressure in the hypertonic saline group.²⁶

- A non-blinded, randomized, controlled trial in adults involving 18 patients in the hypertonic saline group and 16 patients in the control group reported no beneficial effect of hypertonic saline in traumatic brain injury.²⁷

Larger, randomized, controlled trials with meaningful outcomes (mortality and neurological outcome) are needed to determine if hypertonic saline is truly beneficial following traumatic brain injury.

Hypothermia

Hypothermia has been used for over 50 years in the management of patients with traumatic brain injury.²⁸ Hypothermia lowers cerebral blood flow, cerebral metabolic rate, and intracranial pressure.²⁹⁻³¹ One of the mechanisms of action of hypothermia is inhibition of inflammation following brain injury.^{21,32,33}

A meta-analysis of 8 randomized, controlled trials published in the Cochrane database of Systematic reviews in 2000³⁴ showed that active immediate hypothermia therapy led to a 61% reduction ($P = 0.004$) in the odds of death or severe disability. This meta-analysis has been updated recently to include 12 randomized, controlled trials.³⁵ This new meta-analysis demonstrates no benefit from hypothermia therapy.

The conflicting results of these meta-analyses are mainly due to the results of a trial by Clifton³⁶ that showed no benefit from hypothermia therapy. This study was a multicentre trial of 48 hours of moderate hypothermia in 392 adults with severe traumatic brain injury (GCS ≤ 8). There was no significant beneficial effect of hypothermia overall, but hypothermia was beneficial in the patients who presented with hypothermia (core temperature $\leq 35^{\circ}\text{C}$) and age < 45 years. Induced hypothermia led to a higher number of days with complications in those older than 45 years.³⁶ Clifton has subsequently reported large inter-site variability in patient outcomes from this trial³⁷ and poor quality data from the small sites that enrolled few patients. He suggests that this variability may have decreased the power of his study and therefore invalidated the results. Clifton recommends performing a run-in phase at each centre, with protocols for management of blood pressure, cerebral perfusion pressure, and fluid management, as well as ongoing monitoring of compliance with study protocols in trials of therapies for head injury.

At the Children's Hospital of Eastern Ontario, we are conducting a multicentre trial of hypothermia therapy in children and adolescents with severe traumatic brain injury. For more information on our trial, refer to the website: www.cheori.org/Hyp-HIT/hypothermia_in_pediatric_head_in.htm.

Controlling fever

Fever is common following severe traumatic brain injury and the control of temperature and prevention of fever may be important in improving neurological outcome following injury.³⁸ Fay was the first to warn of the deleterious effects of hyperthermia following head injury,²⁸ but there are no controlled studies comparing maintenance of normal temperature in humans with head injury to a control group with no fever control.

There is an acute phase response following moderate and severe brain injury that results in fever.³⁹ Brain temperature has been shown to be higher than body temperature in adults with severe traumatic brain injury.⁴⁰ In children, fever is common and may correlate with worse outcome following head injury.^{38,41,42} Natale et al demonstrated that 58.3% of patients age 3 weeks to 15 years develop early hyperthermia ($T > 38.5$ °C) following severe traumatic brain injury and patients with hyperthermia had lower GCS at discharge from the pediatric intensive care unit.³⁸ In 14 randomized controlled trials of hypothermia in severe traumatic brain injury, temperature was maintained normothermic in the control patients, suggesting that fever control was believed to be beneficial in these patients. There are no reports of adverse effects of fever control for patients with severe traumatic brain injury. It therefore appears prudent to prevent and treat fever aggressively following severe traumatic brain injury.

Decompressive craniectomy

There has been a recent renewal of interest in performing decompressive craniectomy for patients with refractory intracranial hypertension, but without focal masses. Taylor et al reported a randomized trial of early decompressive craniectomy for children with sustained intracranial hypertension following traumatic brain injury.⁴³ Thirteen children received decompression and 14 children received conventional management. There was a

Table 2: Strategies to reduce severity of traumatic brain injury

Recommended strategies

- Airway protection and oxygenation
- Rapid correction of hypotension
- Maintain euvoolemia
- Treat fever

Strategies currently being evaluated

- Corticosteroids
- Hypertonic saline
- Induced hypothermia

Controversial or unproven strategies

- Prophylactic hyperventilation
- Goal-directed therapy to maintain cerebral perfusion pressure

strong trend towards improved outcome in the decompression group. A large, multicentre trial of decompressive craniectomy should be performed to help determine whether decompressive craniectomy should be used for severe traumatic brain injury with refractory intracranial hypertension, but no focal mass lesion.

Conclusion

Following management guidelines or protocols will improve the quality of care and likely improve outcome for patients with a severe head injury. Attention to detail in the prevention and treatment of hypotension and supportive care is very important (Table 2). Cerebral perfusion pressure-directed therapy was not proven to be of benefit in a recent, randomized, controlled trial, and management protocols that ensure maintenance of normovolemia with prevention and rapid reversal of hypotension are likely to be just as effective. Therapies currently being studied with randomized controlled trials include steroids, hypertonic saline, hypothermia and decompressive craniectomy.

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Abstracts of Interest

Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials

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OBJECTIVE: To quantify the effectiveness and safety of corticosteroids in the treatment of acute traumatic brain injury.

DESIGN: Systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury. Summary odds ratios were estimated as an inverse variance weighted average of the odds ratios for each study.

SETTING: Randomised trials available by March 1996.

SUBJECTS: The included trials with outcome data comprised 2073 randomised participants.

RESULTS: The effect of corticosteroids on the risk of death was reported in 13 included trials. The pooled odds ratio for the 13 trials was 0.91 (95% confidence interval 0.74 to 1.12). Pooled absolute risk reduction was 1.8% (-2.5% to 5.7%). For the 10 trials that reported death or disability the pooled odds ratio was 0.90 (0.72 to 1.11). For infections of any type the pooled odds ratio was 0.92 (0.69 to 1.23) and for the seven trials reporting gastrointestinal bleeding it was 1.05 (0.44 to 2.52). With only those trials with the best quality of concealment of allocation, the pooled odds ratio estimates for death and death or disability became closer to unity.

CONCLUSIONS: This systematic review of randomised controlled trials of corticosteroids in acute traumatic brain injury shows that there remains considerable uncertainty over their effects. Neither moderate benefits nor moderate harmful effects can be excluded. The widely practicable nature of the drugs and the importance of the health problem suggest that large simple trials are feasible and worthwhile to establish whether there are any benefits from use of corticosteroids in this setting.

BMJ 1997;314:1855-1859.

Lack of effect of induction of hypothermia after acute brain injury

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BACKGROUND: Induction of hypothermia in patients with brain injury was shown to improve outcomes in small clinical studies, but the results were not definitive. To study this issue, we conducted a multicenter trial comparing the effects of hypothermia with those of normothermia in patients with acute brain injury.

METHODS: The study subjects were 392 patients 16 to 65 years of age with coma after sustaining closed head injuries who were randomly assigned to be treated with hypothermia (body temperature, 33 degrees C), which was initiated within 6 hours after injury and maintained for 48 hours by means of surface cooling, or normothermia. All patients otherwise received standard treatment. The primary outcome measure was functional status six months after the injury.

RESULTS: The mean age of the patients and the type and severity of injury in the two treatment groups were similar. The mean (+/-SD) time from injury to randomization was 4.3+/-1.1 hours in the hypothermia group and 4.1+/-1.2 hours in the

normothermia group, and the mean time from injury to the achievement of the target temperature of 33 degrees C in the hypothermia group was 8.4+/-3.0 hours. The outcome was poor (defined as severe disability, a vegetative state, or death) in 57 percent of the patients in both groups. Mortality was 28 percent in the hypothermia group and 27 percent in the normothermia group (P=0.79). The patients in the hypothermia group had more hospital days with complications than the patients in the normothermia group. Fewer patients in the hypothermia group had high intracranial pressure than in the normothermia group.

CONCLUSIONS: Treatment with hypothermia, with the body temperature reaching 33 degrees C within eight hours after injury, is not effective in improving outcomes in patients with severe brain injury.

N Engl J Med 2001;344(8):556-563.

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