POINT OF VIEW

Use of hypothermia for traumatic brain injury: point of view

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ABSTRACT

Traumatic brain injury (TBI) is one of the major causes of disability in modern society. The World Health Organization has predicted that, by 2020, traffic accidents will represent the greatest burden of global disease and injury. Brain injury after trauma occurs in two stages. Primary injury is directly associated with the biomechanical effects of the trauma, whereas secondary injury occurs later and can be attributed to processes that develop within the brain. Currently, there is no consensus for the use of hypothermia in the treatment of secondary injury after TBI. Until the results of ongoing studies are published, maintaining normothermia and avoiding hyperthermia should be used in managing patient with TBI. *(Minerva Anestesiol 2011;77:366-70)*

Key words: Hypothermia - Traumatic brain injury - Wounds and injuries.

Traumatic brain injury (TBI) is one of the major causes of disability in modern society. The World Health Organization has predicted that, by 2020, traffic accidents will represent the greatest burden of global disease and injury.[1] In 2003 alone, TBI led to 1.2 million emergency department visits and 51,000 deaths in the USA.[2] The long-term consequences of TBI are significant; 2% of the US population require assistance due to disabilities from TBI.

Brain injury after trauma occurs in two stages. Primary injury is directly associated with the biomechanical effects of trauma, whereas secondary injury occurs later and can be attributed to processes that develop within the brain. These processes include the production of oxygen free radicals, cerebral edema with increased intracerebral pressure (ICP), disruption of the blood brain barrier (BBB), and the production of cytotoxic inflammatory mediators in the brain.[3]

The aim of this review was to describe the mechanisms that underlie the use of induced mild hypothermia (32-34 °C) in TBI management and to provide an overview of the most recent studies that have investigated the use of therapeutic hypothermia in TBI management.

Hypothermia

There are several proposed mechanisms by which hypothermia may be neuroprotective. These include the suppression of free radicals, a reduced production of antioxidants in the tissue, protection of the fluidity of lipoprotein membranes, a reduction in oxygen demand in low-flow regions, and a reduction in intracellular acidosis.[4]

Hypothermia lowers the secretion of excitatory amino acids and down-regulates glutamate receptors. Furthermore, it decreases the cerebral metabolic rate by 6-7% for every 1-°C decrease in core temperature, which consequently im-

proves oxygen supply to the areas of ischemic brain and decreases the intracranial pressure.[5] Therapeutic hypothermia exerts a myriad of neuroprotective effects after TBI. Hypothermia (32 °C) has anti-inflammatory effects by inhibiting IL-1B-induced NF-$_K$B activation. IL-1B is a key mediator of endothelial activation, inflammation and secondary brain damage after TBI. Thus, hypothermia suppresses leukocyte rolling adhesion and their eventual infiltration into the injured brain.[6] In a controlled cortical impact model of TBI in rats, mild hypothermia attenuated BBB damage *via* a reduction in free radical-induced microvascular damage.[7] In a fluid-percussion brain injury model in cats, the vasodilatory response to acetylcholine (ACh) was transiently converted to vasoconstriction in the first hours after TBI.[8] Hypothermia followed by slow rewarming was shown to preserve the cerebrovascular response to hypercapnia and ACh in an impact acceleration TBI model.[9] It is most likely that vascular abnormalities and their associated vascular dysfunction to vasodilatory challenges render the brain more susceptible to secondary injury following the initial TBI.[10] Hypothermia also attenuated the axonal injury following TBI[10] and demonstrated a cytoprotective effect against the interstitial increase in aspartate and glutamate after TBI in a controlled cortical impact model.[11]

In contrast, mild hypothermia does not impact cardiac function. Stroke volume and mean arterial blood pressure are not affected, and thus, cerebral perfusion pressure (CPP) can be maintained during TBI.[4, 12, 13]

Therapeutic hypothermia (TH) has been proposed as a therapy in the treatment of TBI based on the premise that decreasing oxygen consumption and intracranial pressure may be protective against secondary brain injury. The first supportive study was conducted by Marion *et al.*[14] which showed a favorable outcome at 12 months in patients assigned to therapeutic hypothermia (32-33 °C) (62% *vs*. 38%) *versus* the control group (P=0.05). However, CT scan scores (with a CT scan score of I representing no visible evidence of injury and a CT scan score of V representing a lesion that required surgical evacuation) between the groups and the interim analysis of 40 patients reduced the confidence in the outcome analysis. Questions about Marion's study led to the development of a randomized controlled trial (RCT) that was reported in 2001 by Clifton *et al.*[15] The study did not show any effect of therapeutic hypothermia on outcome, despite the observation that the hypothermic group showed a significant reduction in ICP. That study has been criticized based on its methodology: treatment was started late, and cooling was slow (average time to target temperature >8 h). Furthermore, there were problems with hypotension, hypovolemia, electrolyte imbalance and hyperglycemia [5] in the treatment group. In his editorial for the study, Marshall criticized the study for intercenter inconsistencies in patient management and the lack of specialized neurointensive care at some of study centers.[16] A *post hoc* analysis of this study found that some subgroups of patients who were hypothermic at admission, ≤45 years old, and were assigned to hypothermia had improved outcomes. Eighty-one patients who were ≤45 years old and were hypothermic (<35 °C) at admission were reviewed. Of this group of patients, those who were assigned to normothermia (and thus were rewarmed) had significantly worse outcomes than did those who were assigned to the hypothermic group (76% *vs*. 52% poor outcomes [P=0.02]).[17, 18] Based on this subgroup analysis, a new study has been initiated that includes hypothermic and normothermic groups of patients with severe TBI (GCS 3-8), in whom hypothermia of 33 °C is being achieved within 4 h after injury and maintained for 48 h in patients who are 16-45 years old. Rewarming is being initiated 48 h after reaching the target temperature. Hypotension will be promptly treated with vasopressors. The results of this study are expected within 2-3 years.[19]

Hutchison *et al*. studied the effect of hypothermia in pediatric patients after TBI.[20] They randomized 108 patients to the hypothermia group (33.1±1.2) and 117 to the normothermia group. The results showed that 31% of the patients in the hypothermia group and 22% in the normothermia group had an unfavorable outcome at 6 months (P=0.14). The mortality rate was 21% in the hypothermic group and 12% in the normothermia group (P=0.06). In another

TABLE I.—*Summary for the major traumatic brain injury trials.*

Study	Age	Study design	Mean temperature of study (°C)	Time to reach target temp (hours)	Time to start after injury	Hypothermia duration (hours)	Results	Problems with study
Clifton [15]	Adult	Randomized trial	32-33	10	N/A	24	No difference between the groups	Intercenter variance in patient management
Hutchison [20]	Children	Randomized trial	33±1.2	10	N/A	24	Increased mortality with TH	• Rapid rewarming during the peak of cerebral edema • More patients in the hypothermic group had hypotension, hypoxia and midline shift
Adelson PD [22]	Children <16	Randomized trial	32-33	Within 6 hr after trauma	N/A	48		Study is ongoing
Clifton [19]	Adults	Randomized trial	33	Within 4 hours	10	48		Study is ongoing
Marion [14]	16-75	Randomized trial	33	Within 10 hours	N/A	24	Favorable	N/A
Aldelson PD [21]	Children <13	Randomized trial	32-33	Within 6 hours	N/A	48	Favorable	N/A

N/A: not available.

study in pediatric patients, Adelson *et al.*[21] did not show any adverse effect of hypothermia on outcome. Based on these conflicting results, the Pediatric Traumatic Brain Injury Consortium Hypothermia Trial is currently underway and is focusing on children who are <16 years old. In this trial, hypothermia (32-33 °C) is being instituted within 6 h of TBI (GCS 5-9) and maintained for 48 h. The study is employing a slow rewarming rate of 1 °C every 12-24 h with pauses in the rewarming during ICP elevations to avoid the problems encountered in previous studies (Table I).[22] In addition to these two ongoing studies in the US, there is a recently initiated pediatric trial in Australia and New Zealand and an adult trial in Japan.[23]

A recent Cochrane analysis evaluated 23 trials with acceptable entry criteria, only eight of which fulfilled the required level of quality. The analysis concluded that there was no beneficial effect of hypothermia in these eight studies. Those studies that were deemed to be of lower quality showed a tendency towards an improved outcome. The Cochrane analysis also showed that the risk of developing pneumonia was higher among patients treated with hypothermia.[24] In contrast, five meta-analyses covering the period 2000-2007 showed a trend towards favorable neurological outcome associated with hypothermia, but only two reviews showed statistically significant results .[25, 26]

Significant methodological differences existed between all of these trials, which may account for the lack of definitive outcome after cooling in TBI trials. Most importantly, the studies lacked uniformity in the timing of the intervention, as well as in the degree and duration of the hypothermia. Furthermore, in the multicenter trials, some of the centers had no previous experience in TH and did not have any specialized neurointensive care units dedicated to the care of TBI patients.

The time to the initiation of cooling was delayed in some trails. It seems obvious that cooling should be initiated as soon as possible after the injury. However, the exact optimum time for this initiation remains unknown. Similarly, the duration of TH should be sufficiently long (at least 48 h) and should be accompanied with a slow rewarming to have a favorable outcome.[25, 27] A recent meta-analysis showed that a reduction in the mortality risk was greatest and favo-

rable neurological outcomes were more common when hypothermia was maintained for more than 48 h following TBI.[28] In particular, a slow rewarming rate might be essential and should be guided not only by the ICP but also by brain-injury biomarker enzymes, such as NSE and S 100 B, and brain chemistry.[29] To date, there have been no randomized controlled trials that assess the best possible rewarming rate.

Some authors have suggested that the introduction of endovascular cooling for rapid induction and proper maintenance of TH and slow, controlled rewarming should be utilized in future trials instead of surface cooling methods.[30] Furthermore, TH should be accompanied with adequate sedation to suppress the hypothermia-induced stress and shivering responses. It was observed that the protective effect of cooling was lost when it was used in unsedated newborn piglets after global anoxia.[31] Significant improvements in outcome were noted when the experiments were repeated in adequately sedated animals.[32] Hypothermia decreases insulin sensitivity and the amounts of insulin secreted by the pancreas. Prevention and/or prompt correction of severe hyperglycemia should be part of the therapeutic strategy during TH to avoid aggravating the neurological injuries.[13, 33] TH induces renal tubular dysfunction, which leads to an increase in the renal excretion of electrolytes during cooling. Hypomagnesemia and hypophosphatemia have been linked to worsening brain injury and increased respiratory problems, respectively.[34, 35] Hypothermic therapy reduces the hypotensive-mediated vasodilatory response; consequently, maintaining adequate CPP during hypothermic therapy is crucial for avoiding potential ischemic insults.[9, 36, 37] Maintenance of normocapnia is important because excessive reduction of cerebral blood flow induced by excessive hypocapnia [38] can increase ischemia in injured brain tissue, and excessive hypercapnia can increase brain edema.[39] In our opinion, based on the plethora of basic science and some evidence from clinical trials, we think that mild therapeutic hypothermia represents an attractive neuroprotective therapy following TBI not only to manage the increases in ICP but also to attenuate the axonal damage and secondary brain injury after TBI. For mild therapeutic hypothermia to be effective following TBI, it should be applied as soon as possible with a slow rewarming rate in specialized neurointensive care centers that have experience in hypothermic therapy.

Conclusions

The supportive evidence for the role of TH in TBI has been disappointing, particularly in the light of recent positive results from clinical trials that involve cardiac arrest.[40, 41] We hope that the development of new trials that focus on younger patients with a more rapid initiation and longer maintenance of TH will prove beneficial. Until then, there remains no proven utility of the initiation of TH in adult patients if the patients are normothermic at the time of admission to the neurointensive care unit and can be managed with the standard methods of treatment. Therefore, the use of TH will be effective in a selected group of patients, especially in those who are hypothermic at admission.

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