Hypothermia in Traumatic Brain Injury

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KEYWORDS

• Hypothermia • Traumatic brain injury • Neuroprotection • Intracranial pressure

KEY POINTS

- Mild to moderate hypothermia reduces the intracranial pressure (ICP).
- Randomized control trials for short-term hypothermia indicate no benefit in outcome after severe traumatic brain injury.
- Longer-term hypothermia could be of benefit by reducing ICP, and ongoing studies may determine this.

INTRODUCTION

Introduction and History

The use of therapeutic hypothermia in clinical medicine has become widely established in the management of cardiac arrest and neonatal hypoxia, whereas the body of evidence in stroke, spinal cord injury, and traumatic brain injury (TBI) remains an ongoing area of active research and discussion.[1,2] Some of the original laboratory studies for TBI used crude methods of cooling, and to temperatures regarded as extreme by current standards. For instance, Rosomoff[3] induced a "closed head injury" in 2 groups of mongrel dogs either at normothermia or at 25°C body temperature, by pouring liquid air into a cylinder in contact with the dura. The hypothermic dogs survived 5 times longer than the normothermic dogs, and this was accompanied by reduced brain swelling. Again, in the laboratory, surface cooling of uninjured dogs to 28°C to 30°C led to a drop in the cerebrospinal fluid (CSF) pressure.[4] Concurrently, several remarkable clinical studies reported instances of the effect of cooling in patients following TBI. Perhaps the first was by Fay,[5] who described therapeutic cooling of the human brain after cerebral trauma as early as 1941, in which he cooled the brain using local irrigation of ice-cold fluids into the cranial vault or cooled systemically using a refrigeration blanket. Some anecdotes that he reported indicate serendipitous, yet remarkable improvement of the patient with cooling (for example, see page 254 of his seminal paper). Around the same time, in a cohort of 30 patients with severe TBI who were cooled, 17 of them survived, which was a large number in the 1950s.[6] To determine the mechanisms that may underlie this improvement, in a controlled study in a small number of patients, the CSF pressure was reduced following hypothermia.[7] These initial groundbreaking studies laid the foundation for hypothermia research in the context of severe TBI and now include the more recent and numerous preclinical mechanistic studies, along with early clinical and more recently larger randomized control trials (RCTs) in an effort to determine whether therapeutic hypothermia is of benefit following severe TBI.

Basic Science Studies

In rodent studies, following a lateral fluid percussion injury, rats undergoing induced hypothermia did better in terms of survival and behavior.[8–10]

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The mechanisms by which this occurs in animal models are multifactorial but include the prevention of secondary brain injury by reducing the excitotoxic, oxidative, and inflammatory effect, by targeting ischemia-reperfusion, and by minimizing cortical depolarization.[11] Hypothermia decreases cerebral metabolic rate and alters release of excitatory neurotransmitters following injury.[12,13] Other mechanisms also include attenuated proinflammatory cytokines, reduced free radicals, and excitotoxic substances.[13,14] Lowering the temperature after TBI has a protective effect on hypoxia-induced cell death.[15–17] Hypothermia also prevents the disruption of the blood brain barrier following injury.[18] Cooling induces a reduction in brain metabolism by 5% per 1°C reduction in core temperature, leading to vasoconstriction and reduced cerebral blood volume, hence a decrease in intracranial pressure (ICP).[19] Moreover, after-injury hypothermia leads to a reduction of chemically induced seizures and spreading depolarizations,[20] and this hypothermia-dependent reduction in seizures has also been reported clinically in TBI patients.[21] Perhaps critically, if the rate of rewarming is too fast, the benefits of reducing the core temperature are lost.[22] With this mechanistic knowledge of the benefits of hypothermia, numerous clinical studies have been undertaken to demonstrate if this treatment modality is ultimately of benefit in the severely injured TBI patient.

TREATMENT OPTIONS

Literature Review

Overview of clinical trials

Clinical trials of hypothermia have 2 broad aims: first, to control the ICP, and second, to provide neuroprotection. As a consequence, the mortality and morbidity outcome determines whether the treatment regimen instigated is of clinical benefit. In general terms, ICP control has been more widely studied in the Far East, whereas primary neuroprotection has been the focus of western clinical trials. The initial western trials involved small patient numbers up to 80. In an early trial, with moderate hypothermia between 32°C and 33°C for 48 hours, a trend toward a better Glasgow Outcome Score (GOS) with a reduction in seizures was observed.[23] In a similar trial, with the same target temperature but for 24 hours, the ICP and cerebral blood flow were lower, and a similar trend toward an improved outcome was observed.[24] In a follow-up study, similar improvements in GOS were observed in patients with a Glasgow Coma Score (GCS) of between 5 and 7, but this difference in GOS was insignificant by 1 year.[25] To evaluate the effect of mild hypothermia (34°C) on ICP in severely head-injured patients, Shiozaki and colleagues[26] in Japan determined that ICP was significantly reduced and cerebral perfusion pressure was increased in those with hypothermia. Hypothermia was continued for at least 2 days, or until it was thought not to be effective. Similarly, reducing the temperature to 35°C resulted in ICP control and improved cerebral perfusion pressure (CPP) in TBI patients, while also reducing metabolism and energy expenditure but maintaining hemodynamic stability.[27] In summary, these small studies were the foundation of larger RCTs to determine the efficacy of hypothermia in the TBI patient.

Short-term hypothermia

With the small case control studies suggesting a benefit of hypothermia in the severely injured TBI patient, the argument for larger RCTs for short-term hypothermia led to several trials in both adult and pediatric populations. The National Acute Brain Injury: Hypothermia (NABIS:H) study was an RCT that had the premise of a neuroprotective strategy so the patients in the treatment group were cooled for 48 hours after injury.[28] The target temperature was 33°C, and the patients were rewarmed at 48 hours irrespective of their ICP. There was no difference in outcome (GOS at 6 months) between the cooled and normothermic groups, although there were significant intercenter differences. The most experienced centers had greater success, using faster cooling times from injury and avoiding hypotension and hypovolemia[29] in the hypothermia group. With these differences between centers, NABIS:H II attempted to address the criticisms of NABIS:H.[30] There were 6 dedicated centers, where patients were rapidly cooled using ice saline within 4 hours of injury. Again, the target temperature was 33°C with rewarming after 48 hours, and the primary outcome was the GOS at 6 months. The trial was terminated early because there was no difference to the null hypothesis, and these 2 studies have been interpreted to suggest that short-term hypothermia does not improve outcome nor provide neuroprotection in TBI. Interestingly, the hypothermia group had more patients with raised ICP and may be in part due to rebound ICP problems because hypothermia was only 48 hours, with ICP problems usually occurring after this during the at-risk swelling phase. Subgroup analysis of the surgical group in which patients had evacuation of an intracerebral hematoma suggested that hypothermia was of benefit, although the number of patients was small (28 surgical cases in which 15 had hypothermia therapy and