A Review of the Use of Early Hypothermia in the Treatment of Traumatic Brain Injuries

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ABSTRACT

Traumatic brain injury (TBI) is an assault to the brain that disrupts neurological activity. Known as the signature wound of combat during Operations Iraqi Freedom (OIF) and Enduing Freedom (OEF), it has become one of the most common injuries to American Soldiers. While affected Soldiers may remain stable after the primary injury, progressing secondary mechanisms can produce neurological degeneration. Hypothermic medicine is the treatment of injuries by cooling the core body temperature below normal physiological levels. Such treatment may be indicated to improve neurological outcomes after traumatic brain injuries by reducing the evolving secondary deterioration.

To date, clinical trials have reached mixed conclusions. Trials have used unique temperature goals for treatment, different methods and times to reach such goals, and different durations at therapeutic temperature. Such variances in procedure and experimental populations have made it difficult to assess significance.

In the article written by Markgraf et al. in 2001, research in animals showed the effect of hypothermic treatment within rats. Their results suggest that early initiation of hypothermic medicine after an induced traumatic brain injury (TBI) improved neurological outcomes when the body was cooled to 30°Celsius (C) within four hours. An ongoing study by Clifton et al., on adults diagnosed with TBI, is examining the neurological outcome of early hypothermic medicine by centrally cooling the body to 33°C and maintaining that temperature for 48 hours.

While previous hypothermic devices were unable to cool rapidly, new technology allows achievement of the goal temperature within 20 minutes. Implementation of such new treatment may show an improvement in neurological outcomes for patients when treatment target temperature is reached within a four-hour window. We recommend that the use of hypothermic medicine should be re-evaluated for its indication in TBI due to the capabilities of a new extremely rapid cooling device.

INTRODUCTION

Traumatic brain injury (TBI) is an insult to the brain that disrupts neurological activity and has become one of the most common injuries to American Soldiers subjected to explosions from improvised explosive devices (IEDs), vehicle borne IEDs (VBIEDs), and suicide bombers. One report indicated that by January 2008, over 5,500 Soldiers had suffered such injury during the Iraq and Afghanistan conflicts.[1] In 2008, about 33% of Soldiers requiring medical evaluation for battle-related injuries who were transported from areas of armed conflict to Walter Reed Army Medical Center (WRAMC) had TBI.[2,3]

Traumatic brain injury occurs most commonly due to proximity to blast explosions as expanding air pressures apply extreme forces to the head, but it can occur with other types of head trauma, such as penetrating wounds, violent physical blows, and from impact with any propelled solid object including shrapnel from explosions or explosively formed penetrators (EFPs). A TBI can also result from rapid accelerations-decelerations of the head due to blast waves even in the absence of an impact from a solid object.[3,4,5]

Mild TBI includes any trauma to the head that may result in loss of consciousness or alterations in mental status. However, the definition of mild TBI is difficult to establish and may only present as headache, dizziness, lack of concentration, or memory loss. Severe TBI is an insult that leaves patients in a persistent coma following medical and surgical therapy.[6]

Multiple factors can initially result in damage at the time of the assault: Nerve fibers can shear in which neurons are stretched and torn, the brain tissue can bruise, and vessels can be compromised producing ischemia or forming destructive pressures.

In addition to the initial disruptions, secondary injuries from multiple elements can lead to new or further neurological deterioration. Increased intracranial pressures (ICPs) are typically at the highest within the

first three days of injury, although one-quarter of TBI patients reached maximal ICPs after day five.[7] Other delayed injuries can be due to factors released during injury that in time induce inflammation, production of free radicals, release of the excitatory neurotransmitter glutamate, electrolyte disturbances of the neuron, and mitochondrial dysfunction.[6] Even though affected Soldiers can be stable and functional after the TBI, these secondary factors can lead to severe neurological deterioration within three to five days post-injury. In standard healthcare, the concentration of care for TBI patients goes into reducing these secondary effects. It would be optimal to prevent secondary injuries in order to prevent secondary neurological damage

Hypothermic medicine, which is the treatment of injuries by cooling the core body temperature below normal physiological levels, was studied in use of brain injuries for over 50 years. Mild hypothermia has been studied extensively in animal models and is defined in humans as the achievement of core body temperatures of 33-34°C. Such treatment may be indicated to improve neurological outcomes after TBI by reducing the evolving secondary injuries through multiple means. One of these was the decrease of cerebral edema and brain swelling.[8] In an animal-model experiment by Markgraf in 2001, early administration of hypothermic treatment within four hours was shown to reduce maximal ICPs at 24 and 48 hours after TBI.[9]

Mild hypothermia may also inhibit the buildup of the neurotransmitter glutamate[10,11] and reduce the metabolic rate of neurons. [8, 12]

Hypothermic medicine may attenuate neuronal death by turning off several chemical pathways of cellular apoptosis.[13,14] Such treatment may also inhibit the inflammatory response by preserving the blood brain barrier[15] or reducing pro-inflammatory cytokines.[16]

After trauma the reperfusion of brain tissue forms free oxygen radicals that damage the cellular membrane of neurons leading to cell death. Hypothermic treatment increases the function of superoxide dismutase, an enzyme that limits the damage of free oxygen radicals and protects the cellular membrane.

Ultimately, hypothermic medicine may assist in the reduction of secondary insults to neurological tissue, perhaps not through all means discovered in the laboratory, but probably through more than one factor described.

Adverse Effects

Treatment with hypothermic medicine carries the adverse risks of cardiac arrhythmia and thrombocytopenia. However, arrhythmia risk is typically only increased during moderate hypothermia, when the body is cooled below 30°C. Since most controlled treatments remain above these temperatures, it is rare to find arrhythmias in hypothermic studies.[17]

Even though it is a common notion that lower body temperatures increase hemorrhage due to impaired function of platelets and coagulation proteins,[18] surgical patients undergoing controlled hypothermia at levels between 32.5 and 33.5°C for cerebral aneurysm clipping showed no greater significant blood loss.[19]

Equipment

Various methods exist with which to administer mild hypothermia; however, to date only surface cooling and intranasal cooling systems have been tested in humans following TBI.[17]

The simplest method of inducing mild hypothermia for treatment is surface cooling. In the past, techniques included applied ice packs and submerging the patient in ice baths to drop core body temperature. The water-circulating surface cooling device consists of blankets placed directly on the patient with regulated cold water circulating through the blankets. The degree of cooling treatment water is determined by feedback from a rectal thermometer. Gel-coated surface cooling devices also exist that work on the same principles as the water-circulating blankets. Only here instead of blankets, transfer pads coated with adhesive gel are attached to the body along the back, abdomen, and bilateral thighs. More recently, helmets and caps have been designed to produce cooling in a more localized area.

Invasive methods such as intravenous cooling consist of a central venous catheter placed within the inferior vena cava. Cooled saline is pushed through the catheter balloons, which are in adjacent contact with the patient's blood. In this procedure the core body temperature is gauged by rectal means. This measured temperature induces a feedback loop that regulates the temperature of the therapeutic saline entering the body. This allows control over therapeutic measures. Another invasive method includes rapid infusion of lactated Ringer's at 4°C combined with surface cooling using ice packs. However, both these invasive methods compromise vasculature access and increase risk of infection and hemorrhage.

In a study by Hoedemaekers et al., it was shown that surface methods of water-circulating blankets and gel pads along with cooled at a rate of 1.33°C/hr, and 1.04°C/hr, respectively. Intravenous cooling with central catheter placement cooled at 1.46°C/hr. These three methods were far more effective than the conventional treatment of running cold lactated ringers solution (0.32°C/hr) and air-circulating cooling systems (0.18°C/hr).[20]

A new ice water immersion system propels and circulates a thin film of ice-cooled water directly around the patient's body in a special molded enclosed environment to reduce core body temperatures at a rate of 4.7°C to 6.6°C/hr. Patients may reach target hypothermic conditions within 20 minutes, at which time the de-

vice can be removed and the core body temperature will remain at a constant lowered value for hours.[21] This portable cooling system is presently the fastest cooling available and is comparable to controlled ice water immersion. (see Figure 1)

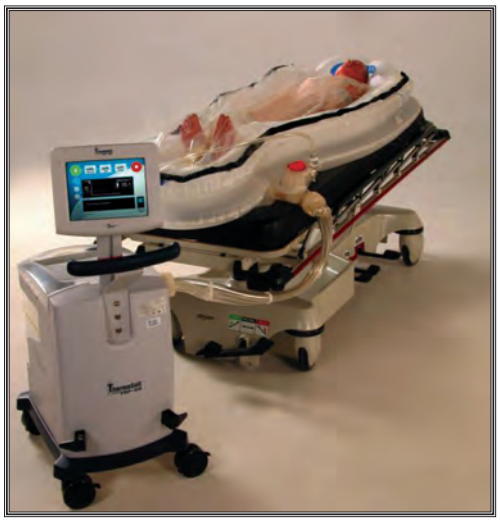

Figure 1: *ICE Immersion*

Trials

To date, clinical results have been conflicting; many reports have been unable to reach proper efficacy in human trials due to a lack of comparable data between control and treatment groups. In association with this, different trials have used unique temperature goals for treatment, different methods and times to reach such goals, and different durations at therapeutic temperature.[22]

In 2001 a clinical trial by Clifton et al. presented no significant neurological outcome difference in severe brain injury patients who were treated with mild hypothermia compared to a normothermic control group. In this study the experimental group reached the therapeutic temperature goal of 33°C in the mean time of 8.4 ± 3.0 hours.[23]

Results of Markgraf et al. (2001) study suggests that early initiation of hypothermic medicine within one hour of an induced traumatic brain injury with rats, improved neurological outcomes when the body was cooled to 30°C. The therapeutic device utilized in this study achieved hypothermic target temperatures within three hours. Overall this meant that target core body temperatures were reached in less than four hours. When initiation occurred after 90 minutes, there was no observed change in neurological outcome.[9]

An ongoing study by Clifton et al. is examining the impact on neurological outcome of using hypothermic medicine to centrally cool the body to 33°C within four hours of traumatic brain injury and then maintaining that temperature for 48 hours.[24]

Conclusion

TBI is considered by many to be the "signature wound" of the present conflicts in Iraq and Afghanistan, thus, further understanding of the mechanisms of injury and the treatment for such is imperative to military medical personnel.

While Soldiers may remain stable after the primary injury, progressing secondary mechanisms can produce neurological degeneration. Results of preliminary studies with hypothermic medicine suggest that this treatment may reduce some of the secondary mechanisms of TBI and also be an effective treatment through other means.

To date the clinical trials of therapeutic hypothermia have given mixed results. Results in animal studies of Markgraf et al. (2001) indicate that early induction of mild hypothermia could produce neuroprotective abilities, when target core body temperatures are reached within four hours after an induced neurological assault. If continued, a National Institute of Health clinical trial by Clifton et al. may be modified to achieve therapeutic temperatures of 33°C with the new fastest cooling portable system clinically available. While previously impossible to obtain such timely new treatment, advances in technology give new opportunities to answer the questions we have posed concerning prevention of secondary injury, and if the data is supportive of this concept, an opportunity to implement a field-ready system that has the potential for forward deployment.

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