Therapeutic hypothermia in brain trauma injury: controversies

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Abstract

Traumatic brain injury (TBI) is a common cause of death and disability in developed countries. It is a major cause of mortality in young patients worldwide. Intracranial hypertension is the cause of death in more than 80% of patients with TBI. When secondary lesions occur, start a number of mechanisms that increase the metabolic injury to brain tissue. Induction of hypothermia has been shown to alter the natural course of the disease process. The biological foundations suggest that hypothermia may have a potential benefit, although some publications have shown no improvement, it is clear that in a group of mostly young patients, early hypothermia may be beneficial. We present a practical review of the literature on this subject.

Key words: Hypothermia, traumatic brain injury, intracranial hypertension.

Introduction

Morbidity and mortality from traumatic injuries are globally recognized as a severe health problem in constant development, these injuries are among the leading causes of death, occurs in all regions, affecting people of all ages and socioeconomic status. (1) Traumatic brain injury (TBI) is a worldwide health problem, (2) according to predictions, the neurotrauma will remain representing a growing number of deaths worldwide by 2020. (3)

Among the TBI secondary lesions are increased intracranial pressure (ICH), release of proinflammatory mediators and free radicals, decreased cerebral blood flow due to systemic hypotension and hypoxia, which are all recognized risk factors for poor outcome. (4–6)

A potential therapy that improves outcomes in specific patient populations is therapeutic hypothermia (TH). (7–11) Hypothermia has been used therapeutically for centuries, (12,13) and has been studied extensively in TBI, (14–26) as a strategy to

improve post-traumatic neurologic outcomes, (2) yet it is one of the few topics that has caused such debate and lack of consensus about its role in this type of injury. (27)

Although there is much information about the pathophysiology of TBI, (28,29) has not yet reached the successful handover of therapeutic interventions seen as promising in animal models to clinical practice. (30) HT is currently recommended by the American Heart Association (AHA), as neuroprotective therapy in the post cardiac arrest care. (13,31) Theoretically it is indicated for the treatment of complications associated with TBI such as ICH (>20mm Hg) and status epilepticus, (32) but is not considered as first-line treatment for TBI in USA, however, it is in use for TBI in 47% of neurotrauma centers in Japan. (33) The aim of this paper is to briefly review some key aspects regarding therapeutic HT in the context of TBI.

Definition

HT is a treatment modality conducted by the physician in order to reduce the core temperature. (13) Hypothermia is defined as a body temperature below 35 ºC (95 °F). It can be classified by their intensity in five groups: (34)

- Mild: 32 a 34º C
- Moderate: 28 a 31.9º C
- Intense: 11 a 28º C.
- Deep: 6 – 10 °C
- Ultradeep: ≤5 °C

History

The use of HT was described by the ancient Egyptians, Greeks and Romans. Hippocrates advised covered with ice and snow in poorly healing wounds to reduce blood loss. Galen also described some uses of HT.

In the 50s, several studies on the physiological effects of HT in humans were conducted, until now no randomized clinical trial. In 1972, Robert Boyle and James Curie and later William Osler attempted to use HT in the treatment of typhoid fever, immersing the patient in icy sea water and brine. Osler reported a 17% reduction in deaths of patients at Johns Hopkins Hospital. (34) In 1814, Napoleon Bonaparte´s General Surgeon, Baron Larrey, described the wounded soldiers were placed near the fires died first than those who were not reheated. (35) The first attempt was made in November 28, 1938. (36, 37)

The potential beneficial effect of HT in the treatment of TBI has been reported since mid-1940. (37) During World War II, the Nazis conducted studies on Jewish men to simulate the conditions suffered by the army and the fallen pilots during wartime, with the objectives to determine the cause of death from hypothermia (cardiac or metabolic), to establish the exact temperature at which the death occurred, determine the best methods of resuscitation, and the most appropriate type of protective clothing. (38–40)

Posteriorly, with the works of Bigelow, the intraoperative HT was used since 1950. (41) Perhaps the most important lesson of the HT history is that it not only seeks to reduce metabolism, but also that mild HT is sufficient, that intensive care in these patients is always necessary, and that the implementation of strategies is needed.

Mechanism of action

To facilitate the use of HT in specific TBI populations is important not only understanding the mechanisms of secondary damage in which the HT mediate, but also the potentially repair mechanisms that can be regulated by hypothermia. (42, 43) HT reduces histopathological damage resulting from the brain injury, to mediate multiple and specific mechanisms of secondary injury as consequence of TBI, such as ICH, (10, 14, 32, 44–46) but the exact mechanisms by which HT has beneficial effects are unknown.

Before 1990 it was felt that the HT-mediated neuroprotection was due to reduced cerebral metabolism. (14) Although such reduction does exist, there are other neuroprotective mechanisms. Decreasing core temperature, so does the metabolic rate, and in turn the consumption of oxygen and glucose, also decreases the production of carbon dioxide, fact that by limiting oxygen delivery, may help to prevent or ameliorate injury. (47) Electrolyte levels are affected due to tubular dysfunction or fluid movement between the intracellular and extracellular spaces.

Although the HT appears to block apoptotic pathways in early stages, there is a small therapeutic window through which the HT can affect this process. (48) HT also reduces or ameliorates the lesion produced by the excitatory neurotransmission. Experimental evidence suggests that the HT decrease ICP through modulation of inflammatory reactions, by reducing cerebral metabolic rate, epileptic discharges and the generation of reactive oxygen species. (49–52) Unfortunately, such theoretical benefits remain as inconclusive in clinical studies. (2)

Metodology to implement hypothermia

There are three commonly recognized phases in the implementation of hypothermia: induction, maintenance and overheating. The purpose of the induction phase is to lower the temperature as fast as possible. In TBI, clinical evidence indicates that the temperature range associated with better outcomes appears to be 32-35°C. (45) It is preferable to reach the maintenance phase quickly because the induction phase may be associated with immediate side effects such as electrolyte disorders, hyperglycemia, and tremor, (53) therefore continuous monitoring of ventilation, blood pressure, sedation, glucose and electrolytes is required.

There are several methods for the induction of TH: (53)

- Surface cooling with air: traditional methods such as skin exposure to air, which can be combined with sponge baths are effective, cooling blankets with airflow are also available.
- Surface cooling with fluids: here are included ice bags, pillows or blankets suits with cooling air circulation, also circulating water pads coated with hydrogel.
- Central Cooling: here are used ice-cold fluid infusions. More invasive devices such as intravascular catheters with balloons full of cold saline. Cold metal components and antipyretic drugs are also used.

Desired temperature is reached more quickly by combining methods. (53)

In the maintenance phase, core temperature must be accurately controlled to maintain stability of the patient. Once at this stage, precautionary measures against side effects of HT should be taken, such as nosocomial infections, or pressure ulcers, especially if therapy is for prolonged time. Rewarming involves slow temperature increase to normal ranges, at a preferred rate of 0.25°C per hour. Should be slow to: (54)

- Minimize electrolyte abnormalities as consequence of movement of fluid between the intra-and extracellular compartments.
- Reduce insulin sensitivity and the risk of hypoglycemia in the case of receiving insulin the patient.
- Prevent exacerbation of injury mechanisms in the injured brain as consequence of the rapid warming.
- Minimizing vasodilation heating degree in order to maintain blood pressure and cerebral perfusion pressure.

Hyperthermia occurs quite commonly after rewarming phase. Normothermia must be maintained because fever is independently associated with adverse outcomes in various forms of brain injury. (53,55–57) Energy crisis and phospholipid degradation occur very easily after TBI in the perilesional tissue. It has been demonstrated by microdialysis studies in patients with severe TBI that mild HT protects perilesional tissues better than to normal brain tissue, to reduce lactate/glucose, lactate/pyruvate ratios and glycerol levels in such areas. (58) Apparently, a high temperature appears not to alter brain neurochemistry substrates and adequate oxygen delivery, (59) however, has been observed that in critically ill patients undergoing hypothermia have less glutamate and lactate/pyruvate ratios, indicating that hypothermia can also participate.

In an animal model of mild TBI was observed that hyperthermia at 39 °C for 15 minutes before the occurrence of injury exacerbates the lesion, causing that mild TBI were vulnerable to cerebrovascular and metabolic processes, such as increased extracellular glutamate concentration, intracellular levels of calcium in the blood-brain barrier and increased inflammation. (60) Hypothermia reduces cerebral metabolism during stress, reduces the release of excitatory neurotransmitters, and reduces the permeability of the blood brain barrier. (61)

Complications

Hypothermia can lead to several complications, including increased risk of infections, electrolyte disturbances such as hypokalemia, hyperkalemia, increased bleeding time, thrombocytopenia, neutropenia, acute renal failure, sepsis, decreased pulse, decreased cardiac output, hypoventilation, CNS depression, hyporeflexia or areflexia, bradycardia, atrial fibrillation, acute pulmonary edema, ventricular fibrillation and asystole. Importantly, many of these complications occur only in cases of severe hypothermia, some have been documented in moderate hypothermia; therefore, the current recommendation is the use of mild hypothermia.

Evidence

The neuroprotective effects of HT in isolated injuries, more often TBI or or spinal cord injury have yielded conflicting results (mortality and functional outcome) in clinical trials. (62, 63) A partial explanation for such conflicting results derived from the different methodological designs used in clinical trials, basically these studies can be divided into those in which the HT was used to treat ICH or studies in which HT was intended to act as neuroprotective therapy to mediate the cease of biochemical and inflammatory cascade, so that comparisons between the studies end controversial. (63)

Specifically in TBI, Harris et al., (64) in their meta-analysis about the role of HT in the management of severe TBI reported no benefit, indeed, Clifton et al., (65) reported a negative effect on the outcome of patients with the same severity of TBI. Polderman et al., (66) demonstrated the effectiveness of HT for the treatment of ICH in patients with severe TBI. In their meta-analysis, Peterson et al., (67) reported a statistically significant reduction in mortality and an increase in favorable neurological outcomes, the benefits were greater in HT maintained for more than 48 hours, however, the increased risk of developing pneumonia opaque favorable findings.

Hutchinson et al., (68) in its international multicenter study showed that in children with severe TBI, HT initiated within 8 hours after the offending event and that continued for 24 hours does not improve neurological outcome, and may even increase mortality. It has also been shown effective not selective cooling systems for achieving desired temperature gradients. (69) Findings like these generate controversy, especially because there are compelling evidence showing benefits of HT in animal models, (14, 70) and human clinical studies have shown the beneficial impact of HT to reduce intracranial pressure, one of the cornerstones in the treatment of TBI. (27, 71, 72)

Georgiou et al., (73) in their meta-analysis on the effect of HT initiated immediately upon admission, mortality and neurologic outcomes in patients with TBI reported the association of HT with cerebrovascular disorders in rewarming, and did not identify benefits on mortality or neurologic morbidity. In a study of 37 patients with severe TBI admitted to ICU, Childs et al., (57) were monitored the behavior of the brain temperature regarding survival. The results support the widespread view that an early increase in temperature of patients with TBI may be associated with poor prognosis, but also suggest an increased risk of death when the temperature is consistently below the "normal" during the first 48h.

The randomized clinical trial 'National Acute Brain Injury Study: Hypothermia II' (NABIS II trial) (42) showed no beneficial effect on the early use of HT in patients with TBI, however an interesting point to consider is the fact that overheating was induced very early, probably increasing the ICP and then worsening outcomes. (23) Currently studies are underway, as the european trial 'EUROTHERM' (ISRCTN34555414), (74) the Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT; NCT00987688).

According to guidelines issued by the Brain Trauma Foundation /American Association of Neurological Surgeons, the optional and cautious use of HT in adults with TBI is a level III recommendation. (5)

Conclusions

Most of the evidence for the neuroprotective effects of mild to moderate HT derived from animal research models, their clinical role is still undefined, so human studies are needed to clarify its real therapeutic effect. (62)

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