Hypothermia for neuroprotection in severe traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is a common cause of morbidity and mortality worldwide. There has been a constant search for therapeutic modalities in an attempt to reduce this burden, but till date, none of them have proved to have a significant clinical impact. The interest in whole-body hypothermia as a treatment modality for severe TBI arose from enthusiastic experiences with the patients having anoxic brain damage after cardiac arrest. However, despite numerous randomised controlled trials (RCTs) and systematic reviews, its role in improving the outcomes after TBI are still far from being certain to warrant its clinical usage. The concept that hypothermia may be beneficial in improving the outcomes after TBI evolved with the discovery that the final neuronal injury pattern after an ischemic event could be lessened by cooling the brain. Several subsequent animal studies and clinical trials have now been conducted, which have led the Brain Trauma Foundation to issue a Level III recommendation for the use of primary therapeutic hypothermia in the management of TBI. Induced hypothermia should logically be useful in improving the mortality and neurologic outcome after severe TBI. However, the beneficial, effect of hypothermia only exists in high-quality trials, and presently, there is no Level I or Level II evidence. The relative scarcity of high-quality data in this setting entails well-designed large multicentric RCT's to prove any association if it exists.

Key words: Hypothermia, mortality, neuroprotection, outcome, traumatic brain injury

INTRODUCTION

The interest in hypothermia as a therapeutic modality dates back to 5000 years back when it was mentioned in the Edwin Smith Papyrus, an ancient Egyptian treatise.[1] Hippocrates recommended ice packing of the wounded to reduce haemorrhage.[2] Sir William Osler used hypothermia in typhoid fever and reported a decline in mortality from 24.2% to 7.1%.[1] The application of therapeutic hypothermia to modern medicine is credited to Fay, who treated a female patient with intractable pain from metastatic breast cancer, by cooling her to 32°C for 24 h.[3] Rosomoff and Holaday in 1954s demonstrated that cooling reduced the cerebral blood flow and oxygen consumption and had a beneficial effect on intracranial pressure (ICP) in experimental studies.[4] Induced hypothermia is presently an accepted modality to improve the patient outcomes after anoxic injury associated with cardiac arrest;[5,6] however, its benefits in traumatic brain injury (TBI) are uncertain.

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MECHANISM OF NEUROPROTECTION

Cerebral metabolic rate decreases by about 6–7% for every 1°C drop in temperature,[9] thereby reducing the oxygen demand, preserving the phosphate compounds and energy stores, preventing lactate production and development of acidosis.[10,11] Immediately after TBI, hypothermia is known to improve the brain glucose utilisation.[12] Cerebral blood flow decreases commensurately with cerebral oxygen consumption during hypothermia, suggesting preservation of autoregulation.[10] The major acute effect of hypothermia on cerebral blood

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flow appears to be the prevention of hyperaemia after the reperfusion.[10] Brain injury triggers the release of excitatory amino acids and glutamate, which are responsible for excitotoxicity.[13] Hypothermia is known to prevent the release of these excitatory amino acids[14] and down-regulates astrocytic glutamate transporter I, which mediates the reverse transport of glutamate and attenuates glutamate receptor expression.[15] Hypothermia also prevents the glutamate-induced increase of nitric oxide synthesis and suppresses N-methyl-d-aspartate receptor phosphorylation.[16]

In the subacute phase after TBI, many secondary injury mechanisms are happening such as the cellular apoptosis, inflammation, generation of reactive oxygen species (ROS) which lead to the disruption of blood brain barrier and oedema formation.[13] Hypothermia prevents the ischemia-reperfusion triggered release of ROS and has been shown to have a suppressive effect on inflammation and mitigates the release of inflammatory markers by reducing the astrocytic and microglial activation.[9,17] Furthermore, hypothermia also attenuates the release of proapoptotic mediators and activates antiapoptotic pathways.[18] The most important effect of hypothermia is the preservation of the blood brain barrier after TBI that helps in limiting the brain oedema and further ICP increase.[9,13] Finally, in the chronic phase after TBI, hypothermia also appears to have a role in the neuronal regeneration and neural circuit repair, although this remains an active area of research till now.[13]

PHYSIOLOGICAL EFFECTS OF HYPOTHERMIA

The therapeutic hypothermia consists of three phases-induction, maintenance and rewarming; each of which are associated with their own risks.[9] The rates of different biochemical reactions in the body are determined by temperature, substrate concentration and pH. Hypothermia, therefore, affects all the biological processes in the body.

CARDIOVASCULAR EFFECTS

Hypothermia is known to cause a decrease in the heart rate, with an associated improvement of left ventricular filling and a positive inotropic effect. The incidence of arrhythmias generally does not increase at temperatures more than 30°C.[9,19] Other effects include an increase of systemic vascular resistance due to cooling-induced peripheral vasoconstriction and the consequent increase in the cardiac output and mean arterial pressure.[9,18] The increase in the venous return leads to release of atrial natriuretic peptide and decreased levels of antidiuretic hormone leading to 'cold diuresis'.[19] A reasonable fluid challenge should be given if hypotension develops during the induction phase.[9]

PULMONARY EFFECTS AND INFECTIVE COMPLICATIONS

Acute respiratory distress syndrome (ARDS) and neurogenic pulmonary oedema develop in about a third of all intubated neurologic patients.[20,21] However, ARDS develops in less than half of the hypothermic patients as compared to those having normothermia.[22] There has been a controversy regarding the increase in the infectious complications and development of pneumonia in hypothermic patients, due to the inhibition of the inflammatory response by hypothermia. However, studies involving prolonged hypothermia reported no difference in infectious complications as compared to controls.[23,24]

HEMATOLOGIC FUNCTION

The effect of hypothermia on the coagulation is perhaps the most concerning factor with the coagulation cascade being affected at temperatures <33°C and platelet function decreased at <35°C.[9] The prolongation of activated partial thromboplastin time (aPTT) is controversial, however, close aPTT monitoring is recommended.

RENAL, ENDOCRINE AND GASTROINTESTINAL EFFECTS

Electrolyte disorders especially hypokalaemia and hypomagnesaemia occur during the induction phase. Hence, slow rewarming is recommended as it is associated with hyperkalaemia. The myocardial sensitivity to potassium increases during hypothermia, hence, hypokalaemia is protective.[24]

The insulin sensitivity is decreased leading to a reduction in insulin secretion and consequent hyperglycaemia, especially during the induction phase. Hypothermia may promote bowel ileus and delayed gastric emptying.[18]

LIVER FUNCTION AND DRUG METABOLISM

Hypothermia affects the rates of renal tubular secretion and reabsorption with overall reductions in activities of several enzyme systems including cytochrome p450.[25] There is a reduction in drug clearance of commonly used medications like vasopressors, phenytoin, sedatives, opiates, etc.[9]

ROLE OF HYPOTHERMIA IN TRAUMATIC BRAIN INJURY WITH CURRENTLY AVAILABLE EVIDENCE

Traumatic brain injury is a major cause of death and disability worldwide, associated with a huge social and financial burden to the society. The death and disability after TBI are due to a combination of the effects of the primary brain injury due to the shearing and damage of the neurons and glial cells at the time of impact; and the development of the secondary brain injury, which occurs due to the effects of ischaemia and reperfusion injury, soon after the impact. The cerebral ischemia develops due to the increased ICP, cerebral hypoperfusion, impaired autoregulation, disturbed blood-brain barrier and increased cerebral metabolic demand. The reperfusion injury is due to a complex cascade of events finally leading to apoptosis and programmed cell death. Hypothermia may be theoretically beneficial in TBI by interrupting this destructive cascade of cellular events as already mentioned above.

There has been a constant search for strategies to improve the outcomes after TBI, which may play a pivotal role in the future in the acute management of patients suffering from TBI. Several studies over the past decade have focused to accumulate the evidence supporting the use of induced hypothermia for TBI. Although the effect of hypothermia in TBI was first published by Fay[3] in 1945, very little progress has been made in this field till the publication of two landmark trials published in 1993, suggesting a statistically significant benefit from mild to moderate hypothermia in improving the survival and neurologic outcome after TBI.[26,27] Thereafter, another much anticipated randomised controlled trial (RCT) (National Acute Brain Injury Study-Hypothermia [NABIS-H] trial) of therapeutic hypothermia in 392 patients did not find any beneficial effect on the outcome of patients with TBI, although, on the contrary, found more incidences of hypotension and increased number of days with critical complications in hypothermia group.[28] The patients were cooled to 33°C for a period of 48 h. This trial was intended to recruit a total of 500 patients but was terminated on grounds of futility. The subgroup analysis revealed a trend toward worse outcomes in elderly patients >45 years of age and in patients who were hypothermic at admission and then rewarmed. Moreover, patients <45 years presenting with hypothermia and not rewarmed, did well. The lessons learnt from this trial suggest that there may be a narrow therapeutic window for hypothermia to act. Since the publication of this trial, numerous other studies have been published with conflicting evidence in the literature. These studies can be divided into two broad categories: (i) Prophylactic hypothermia-studies with protocols for cooling at 33–34°C for a predetermined short period of 24–48 h, irrespective of the ICP; and (ii) therapeutic hypothermia - with study protocols for cooling to longer periods of time or until ICP normalises. All the studies on prophylactic hypothermia have so far failed to show a better outcome,[26-28] however, some studies on therapeutic hypothermia have reported decreased mortality and improved neurological outcomes in TBI.[29-33] There may be a theoretical benefit in cooling for longer periods of time as the cerebral oedema and the reperfusion injury peaks at 3–5 days after TBI and may last for several days beyond that.

The Brain Trauma Foundation laid down guidelines for the management of severe TBI and issued a Level III recommendation for the use of primary therapeutic hypothermia in the management of severe TBI.[8] These recommendations were based upon six moderate quality (Level II) trials included in the meta-analysis. They concluded that the risk of all-cause mortality for patients treated with mild hypothermia is no different than that from the normothermia group. However, hypothermia is associated with a 46% increased chances of a good outcome. The mild hypothermia may have higher chances of reducing mortality when cooling is maintained for more than 48 h.

A multicentric RCT of very early hypothermia induction was published by Clifton *et al.* (NABIS-H II study).[34] The patients were enrolled within 2–2.5 h after injury and mild hypothermia was induced (33°C) for a period of 48 h. A total of 232 patients could be randomised in the study, and the trial was terminated for futility. The authors found no difference in outcome and mortality in the hypothermia group and the trial did not confirm the utility of hypothermia as a primary neuroprotective strategy in TBI.

There have been several RCTs after the trials by Clifton *et al.*[26] and Marion *et al.*[27] assessing the role of mild hypothermia in TBI [Table 1]. Most of these trials were of a low quality.[27,28,30,32-36] None of the two high-quality trials[34,37] and one moderate-quality trial[26] showed any benefit from hypothermia in terms of improving the outcome after severe TBI. However, there was improvement in patients in those low-quality trials in which hypothermia was maintained for a longer duration of >48 h.[30,33-36]

Over the last decade, there have been several attempts at collating the data from the RCTs and have resulted

in the publication of a meta-analysis on the use of mild hypothermia in TBI [Table 2].[41-48] The most comprehensive analysis has been by Cochrane group by Sydenham *et al.*[47] The analysis included 23 RCT's involving a total of 1614 patients. There was again an overall significant benefit in terms of mortality and neurological morbidity only in low-quality trials, which was lost when high-quality trials were analysed. The authors concluded that this improvement might be a play of chance and suggested that hypothermia should not be used except in the context of a high-quality RCT with good allocation concealment.

A more recent systematic review delineated the effects of mild hypothermia in severe TBI.[49] The authors included a total of 18 RCT's in their analysis. These RCT's were assessed for their robustness using Grading of Recommendations Assessment, Development and Evaluation system of assessment.[50] The methodological flaws responsible for downgrading of the trial evidence were absence of allocation concealment, adequate outcome assessor blinding, a small number of patients, absence of detailed important treatment variables and heterogenous baseline variables. The overall relative risk (RR) of mortality and poor neurologic outcome with hypothermia as compared to controls was 0.84 and 0.81, respectively. However, when only high-quality trials were analysed, the RR were 1.28 and 1.07, respectively. Furthermore, hypothermia was associated with reduced cerebral perfusion pressure on rewarming and increased chances of pneumonia. The authors concluded that there is no benefit of hypothermia on mortality or neurologic outcome in patients with severe TBI.

The controversy regarding the beneficial effect of hypothermia on the outcome in patients with severe TBI still persists after more than 40 animal trials[51] and so many clinical trials and systematic reviews published in literature so far. The human trials have lacked the methodological robustness and adequate power required to detect any benefit. The heterogenous nature of TBI has added to the problem in evaluating the role of hypothermia. The peak rise in ICP occurs after 48 h in TBI, when several trials have already started rewarming during the peak of alterations in cerebral metabolism, thereby opposing any beneficial effects of hypothermia, should one exist.[31,35,37-39] Furthermore, the peak neuronal death occurs within hours after TBI. However, the target temperature was achieved within 8 h only in some trials.[28,34,37] Finally, Glasgow outcome score (GOS) is a crude assessment measure of outcome,

Table 1: Summary of published articles on mild hypothermia in TBI

Author/Journal/Year	Number of patients	Target temperature/ duration of HTH	Mortality reduction	Improvement in neurological outcome
Clifton *et al.*[34] Lancet 2011 (NABIS: H II Trial)	97	33/48	No	No
Hutchison *et al.*[37] NEJM 2008 (HiTBIC Trial)	225	32.5/24	No	No
Qiu *et al.*[31] J Crit Care 2007	80	33-35/96	No	Yes
Adelson *et al.*[36] Neurosurgery 2005 (Cool Kids Trial) HYPO I and II	(48 hypo I)/26 (hypo II)	32-33/48	No	No
Qiu *et al.*[38] Chin J Traumatology 2005	86	33-35/103	Yes	Yes
Smrcka *et al.*[39] Acta Neurochirur 2005	72	34/72	No	Yes
Zhi *et al.*[40] Surg neurology 2003	396	32-35/62.4	Yes	Yes
Clifton *et al.*[28] NEJM 2001 (NABIS: H Trial)	392	33/48	No	No
Shiozaki *et al.*[35] J Neurosurg 2001	91	34/48	No	No
Jiang *et al.*[29] J Neurosurg 2000	87	33-35/72-336	Yes	Yes
Clifton *et al.*[26] J Neurotrauma 1993	46	32/48	No	No
Marion *et al.*[27] NEJM 1993	82	32/24	No	No

HTH – High-temperature hyperthermia; TBI – Traumatic brain injury

Table 2: Summary of published meta-analysis on hypothermia in TBI

Author/Journal/Year	Number of trials analysed	Number of patients	Mortality reduction	Improvement in neurological outcome
Fox *et al.*[42] CJEM. 2010	12	1327	Yes	Yes
Sydenham *et al.*[47] The Cochrane database of systematic reviews 2009	21	1587	Yes	Yes
Peterson *et al.*[46] J Neurotrauma 2008	13	1339	Yes	Yes
Henderson *et al.*[44] Intens Care Med 2003	8	748	Yes	Yes
McIntyre *et al.*[45] JAMA 2003	12	1069	Yes	Yes
Harris *et al.*[43] Arch Neurol 2002	7	668		Yes

TBI – Traumatic brain injury

which might miss subtle differences. Hence, a more detailed outcome measure may involve the use of GOS extended (GOSE).[52]

Henceforth, in order to address the controversial issue of the role of hypothermia in severe TBI, future hypothermia trials should consider the initiation of hypothermia in prehospital setting, maintenance of cooling for more than 48 h, rewarming according to physiological rather than time-based criteria and follow-up based on GOSE scores. The results of the on-going trials such as polar-RCT and Eurotherm-3235 are eagerly anticipated to solve many such issues pertaining to this topic.[53,54]

CONCLUSION

Hypothermia should logically be useful in improving the mortality and neurologic outcome after severe TBI. The beneficial, effect of hypothermia has only been shown to exist in high-quality trials so far, and presently, there is no Level I or Level II evidence to support its clinical use. The relative scarcity of high-quality data in this setting entails well-designed large multicentric RCT's to prove any association if it exists.

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