Active cooling in traumatic brain-injured patients — a questionable therapy?

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Short title: Hypothermia in severe TBI

Abstract

Hypothermia is shown to be beneficial for the outcome after a transient global brain ischaemia through its neuroprotective effect. Whether this is the case also after focal ischaemia, such as following a severe traumatic brain injury (TBI), has been investigated in numerous studies, some of which have shown a tendency of improved outcome, whereas others have not been able to demonstrate any beneficial effect. A Cochrane report concluded that the majority of the trials already published have been of low quality, with unclear allocation concealment. If only high-quality trials are considered, TBI patients treated with active cooling were more likely to die, a conclusion supported by a recent high-quality Canadian trial on children. Still, there is a belief that a modified protocol with shorter time from the accident to the start of active cooling, longer cooling and rewarming time, and better control of blood pressure and ICP would be of benefit for TBI patients. This belief has led to the instigation of new trials in adults and in children, including these types of protocol adjustments. The present review gives a short summary of our present knowledge of the use of active cooling in TBI patients, and presents some tentative explanations as to why active cooling has not been shown to be effective for outcome after TBI. We focus particularly on the compromised circulation of the penumbra zone, which may be further reduced by stress caused by the difference in thermostat and body temperature and by the hypothermia-induced use of vasoconstrictors, and by the increased risk of contusional bleedings under hypothermia. We suggest that high fever should be reduced pharmacologically.

Key words: hypothermia, focal ischemia, global ischemia, thermostat, contusional bleedings, fever, body temperature, penumbra zone, cerebral circulation

Introduction

It has been well known for long from several experimental studies, that hypothermia is neuroprotective following brain ischaemia.[1,2] A protective effect of hypothermia is also apparent from the experience that near-drowning in cold water in the winter has unexpectedly good outcome. [3-5]. The rate of the negative cascade of pathophysiological alterations initiated by ischaemia is no doubt temperature-dependent. There are also strong indications from the literature that fever is associated with adverse effects in the brain-injured patient.[6] The mechanisms by which hypothermia exerts its neuroprotective effect are, however, still far from clear. Protective factors may be the hypothermia-induced reduction in brain metabolism, prevention of apoptosis, reduced mitochondrial dysfunction, a reduced production of free radicals and also reduction in oxidative DNA damage and in pro-death signalling events.[2,7]

There are rather strong indications from clinical studies that moderate hypothermia (32–35°C) is beneficial for outcome following a global brain ischaemia, such as after cardiac arrest [8,9] or following neonatal asphyxia.[7,10] In light of the demonstrated and generally accepted neuroprotective effect of hypothermia in global ischaemia, and also the fact that animal studies have indicated that there may be beneficial effects also in focal ischaemia, such as after a head trauma,[7,11] the expectation that hypothermia would also be a valuable treatment for patients with focal brain ischemia has been great. Such patients would be those with ischaemic and haemorrhagic stroke, patients with intracerebral hemorrhages and patients who have suffered a severe traumatic brain injury (TBI).[7] Hypothermia is also believed to be a valuable tool in controlling an elevated intracranial pressure (ICP) and a way of moderating the biochemical cascade involved in secondary brain injury.[12,13] However, in

spite of several clinical trials from mainly high-quality modern intensive care units, we still lack any evidence for the view that hypothermia is a successful treatment after focal ischaemia, such as after a TBI. An overview of the use of hypothermia after a brain injury were recently published in a special hypothermia issue of the Journal of Neurotrauma.[14]

In this review, we give a short summary of the current status of the use of hypothermia in TBI patients and discuss tentatively why there is still a lack scientific evidence for the hypothesis that the documented neuroprotective effect of active cooling under global ischaemia can also be used successfully after a severe TBI.

Key studies from the past decades

Several studies have been published both in children and in adults during the last decade, evaluating the effect of hypothermia on outcome following a severe TBI. Even though some of these studies showed improved outcome or a trend of improved outcome from hypothermia, few of them fulfill the requirement of acceptable quality. For example, some were preliminary studies involving insufficient numbers of patients, some were not properly randomised, and others suffered from shortcomings in protocols and methodology. Two relatively well-performed randomised studies in children[13,15] could not demonstrate any beneficial effect of hypothermia on outcome. In a single-centre randomised trial by Marion et al.[16] on adults, they found that a 24-h treatment with hypothermia improved outcome only in a subgroup of patients with a Glasgow Coma Score (GCS) of 5–7. In an attempt to dispel the uncertainty regarding the use of hypothermia in severely injured TBI patients, Clinton et al. performed a methodologically well-designed, National Institute of Health (NIH)-supported large randomised phase III trial on adults between 16 and 65 years[17] with a GCS of 8 or less. The study showed the same mortality rate in the normothermia group and the hypothermia

group for the whole material. In a subgroup of patients between 16 and 45 years of age, however, there was a tendency of better outcome in the hypothermia group, whereas outcome tended to be worse in patients aged between 45 and 65 years.

A recent randomised multicentre study in children

Due to the lack of large randomised multicentre studies on the effect of hypothermia in children suffering a severe TBI, a multicentre study involving 225 children with a GCS of 8 or less from 17 centres in 3 countries was performed. The results from this Canadian study were presented by Hutchison et al. in the New England Journal of Medicine in 2008.[18] They found no statistically significant difference in outcome between the hypothermia group and the normothermia group for the whole material, but there was a clear tendency of worse outcome in the hypothermia group. Due to the unexpected negative results from this properly designed study, it will be described in more detail below.

One hundred and eight patients were randomly assigned to the hypothermia group and 117 to the normothermia group. They were cooled with a surface cooling technique and the oesophageal temperature was maintaind at 33.1 ± 1.2°C for 24 h. The mean time to initiation of cooling was 6.3 ± 2.3 h after injury and the mean time to completion of rewarming after the 24-h cooling period was 18.8 ± 14.9 h. The 2 groups did not differ otherwise except that more hypertonic saline was given to the normothermia group for treatment of ICP, and more vasoactive drugs were given to the hypothermia group to maintain an adequate blood pressure. The results showed that 31% of patients in the hypothermia group and 22% in the normothermia group had unfavorable outcome at 6 months ($p = 0.14$). Mortality rate was 21% in the hypothermia group and 12% in the normothermia group ($p = 0.06$). In a subgroup of patients older than 7 years, there was a higher mortality rate in the hypothermia group ($p <$

0.03). ICP was lower during the cooling period and higher during the rewarming period as compared to the normothermia group. The fact that patients with ICP below 20 mmHg had significantly worse outcome in the hypothermia group ($p < 0.03$), in spite of the beneficial effect inherent in a lower ICP, indicates that mechanisms other than those related to ICP were responsible for outcome in this study. The successive improvement up to 12 months was also greater in the normothermia than in the hypothermia group according to a specific scoring system ($p = 0.07$). Twelve months after injury, scores on assessment of long-term visual memory were worse in the hypothermia group than in the normothermia group ($p = 0.05$). This study strongly supports the view that hypothermia treatment according to the protocol used has adverse effects on outcome in TBI patients.

Cochrane analysis

A recent Cochrane meta-analysis of the effects of hypothermia in TBI patients evaluated the effect of using moderate hypothermia to a body temperature below 35°C on outcome in TBI patients.[19] The Cochrane analysis evaluated 23 trials with acceptable entry criteria, only 8 of which fulfilled the required level of quality. It was concluded that there was no beneficial effect of hypothermia in the best 8 studies, while those with a low quality showed a tendency of improved outcome. Thus, the majority of trials were of low quality with unclear allocation concealment and they were not properly randomised; it was proposed that these low-quality studies may have overestimated the effectiveness of hypothermia treatment relative to the control treatment. In studies with good allocation concealment, patients who received hypothermia were slightly more prone to die. The Cochrane analysis also showed that the risk of developing pneumonia was higher under hypothermia. It was concluded that there is no evidence so far for the view that hypothermia improves outcome following a TBI.

Can alternative protocols improve outcome?

In the wake of the reports of negative results from clinical hypothermia TBI studies, the discussion has concentrated on the possibility of better outcome if the protocols for the hypothermia group are changed. It may be that negative effects of the cooling and rewarming procedure overshadow the neuroprotective and other positive effects. For example, the chances of the hypothermia therapy having proper effect would be reduced if the time-delay from the primary injury until start of the cooling was too long. Rewarming can lead to vasodilation and to a rebound increase in ICP, especially when the post-traumatic hypothermia period and the rewarming period are short. The tendency of an overshoot of the temperature during and after the rewarming phase may also be a complicating factor, as is the hypothermia-induced increased frequency of infections.[19] Further, the brain oedema has normally reached its maximum 3-4 days after injury, a point of time when the "protective" cooling period has been finished. From these considerations, it has been speculated that a shorter time delay before the start of cooling after the accident, a faster cooling, and a more long-term cooling period followed by an extended rewarming phase may give improved outcome.[7,20-23] Clinical data have shown that hypothermia reduces an elevated ICP, most likely via reduced intracranial blood volume. Perhaps the rebound increase in ICP during the rewarming phase abolishes this positive effect, which may explain why there are still no data to support the view that the hypothermia-induced ICP reduction improves outcome.[13] The question may be raised as to whether an intracranial blood volume-reducing therapy induced by hypothermia would be as effective as the established ICP-reducing therapies, which mainly act by reducing brain oedema.[24-26]

Ongoing studies

The Clifton study[17] has been criticised for limitations such as the excessive time delay before cooling after the accident and for uneven distribution of the results between different centres.[27] With their experience from this study,[17] a new study on adults was initiated by the same group with the following protocol: a hypothermia group and a normothermia group of patients with severe traumatic brain injury (Glasgow Coma Scale 3-8), in which the hypothermia of 33°C is reached within 4 h after injury and maintained for 48 h in patients aged 16–45 years. Rewarming is started 48 h after the patient has reached 33°C. Hypotension is actively counteracted by the use of vasopressors. The aim of the study is to analyse outcome in terms of Glasgow Outcome Score 3, 6 and 12 months after the brain injury. Only 6 centres are involved. The results of the study are expected within 2–3 years from now.[28]

Attempts were made by the authors of the Canadian paediatric study by Hutchison et al.[18] to explain the negative results by the lack of uniform clinical management, variability in time to initiation of cooling, the relatively short cooling duration of 24 h, the relatively short rewarming period of about 19 h on average, and by the increase in ICP during the rewarming period. Concerns have been raised regarding the difference in results between this study and the paedriatic study by Adelson et al.,[15] which did not show any adverse effect of hypothermia on outcome.

Based on the experience gained from these paediatric studies,[15,18] a new paediatric trial is now underway;[29] it concentrates on children less than 16 years and is called the “Pediatric Traumatic Brain Injury Consortium Hypothermia Trial”. The criteria in this trial reflect the subgroup in the previous study by Adelson et al.[15] with the best response to hypothermia treatment. The primary hypothesis in the new trial is that early cooling within 6 h of injury to 32–33°C after a severe TBI (GCS 5–9) and maintainence of that temperature for 48 h will

reduce mortality compared to normothermia (37–38°C). A rewarming rate of 1°C every 12–24 h with halts in rewarming at ICP elevations means a slower rewarming rate than in previous studies. [29]

Apart from these 2 ongoing studies from the United States, there is a recently initiated paediatric trial in Australia and New Zealand and an adult clinical trial in Japan,[30] also investigating whether a modulation of the protocols might improve outcome.

Tentative explanations for the lack of improved outcome after cooling in TBI patients

It is unlikely that the lack of beneficial effects of hypothermia on outcome in TBI patients can be explained only by weaknesses in the protocols used so far, as similar protocols have been shown to be effective in global ischaemia.[8-10] Four negative consequences of hypothermia in TBI patients, based on the specific cerebral pathophysiology characterising these patients, will be presented below, which may explain why hypothermia treatment has not been shown to be effective for outcome — or even may aggravate the outcome in TBI patients. They are *(1)* the effect of hypothermia-induced stress on the microcirculation of the penumbra zone, *(2)* side effects of the more frequent use of vasoconstrictors due to decrease in blood pressure following cooling, *(3)* the risk of increased contusional bleedings due to hypothermia-induced coagulopathy, and *(4)* the danger associated with increase in ICP during the rewarming period in patients with a raised ICP.

Hypothermia-induced stress response

Active cooling always means a difference between the body temperature and the temperature stipulated by the thermostat. This difference creates a metabolic stress response aimed at restitution of temperature to the level prevailing before the start of cooling, and this stress

response will continue as long as there is a difference between thermostat and body temperature.[31, 32] Muscle shivering is a visible component in this stress response, but the stress also means an increase in the release of cathecholamines to plasma. People who have been awake with severe sepsis, with relatively fast fluctuations of body temperature, have born witness to an excruciating amount of stress related to the period of increasing temperature towards the higher temperature stipulated by the thermostat.

Outside the injured parts of the brain, the cerebral circulation is sufficiently adequate to avoid severe hypoxia. Only a smaller part of the traumatized brain, the contusion and its nearest area, the penumbra zone, is hypoxic. Most likely, the compromised microcirculation of the penumbra zone that results in hypoxia may persist for days and may even be permanent. The penumbra zone with its potentially salvable cells is a most essential area for outcome after a severe TBI. The lowered temperature will reduce cerebral circulation in the whole brain in direct relation to the decrease in brain metabolism. However, the large stress response with increased levels of cathecholamines may superimpose further vasoconstriction, and further reduce the already compromised circulation of the penumbra zone.[26,33,34] This means that the hypoxia can be aggravated in the penumbra zone and potentially salvable cells will die even though oxygen demand is reduced at a lower temperature. The cooling-induced metabolic stress maybe one limiting step in demonstrating the benefits of therapeutic temperature modulation in head injured patients.

From this point of view, the head trauma patient is different from patients with transient global cerebral ischaemia, such as after drowning in cold water in the winter, in patients with a transient cardiac arrest or after neonatal asphyxia.[3,9,10] The neuroprotective effects of hypothermia can act on a brain with normal perfusion, where the injured – but not dead –

brain cells have the potential for restitution and regeneration. Under these circumstances, hypothermia for example may counteract the negative effects of free radicals released when the perfusion is restored, and reduce the risk of apoptosis.[7] The possibility of utilising the neuroprotective effects of hypothermia following a very short period of global cerebral hypoxia may therefore be much greater than after a severe head trauma with contusion and penumbra zone areas, in which a compromised circulation will last for a long time and it will be reduced further by active cooling.

Hypothermia-induced use of vasoconstrictors

Hypothermia means reduction in arterial blood pressure, which has resulted in more frequent use of vasocontrictors in patients exposed to hypothermia than in patients with normothermia.[18] The use of vasoconstrictors is an important component to counteract hypothermia-induced reduction in arterial pressure in the ongoing study by Clifton et al.[28] Even though the use of vasoconstrictors is common in the treatment of TBI patients and favoured in traditional guidelines to increase cerebral perfusion pressure,[24,25] serious concerns have been raised since almost 2 decades in the use of these drugs in TBI patients, as they may compromise the circulation further of the hypoxic penumbra zone.[26,27] A recent study even showed that cerebral oxygenation was negatively affected by infusion of norepinephrine in healthy subjects.[34]

Hypothermia-induced coagulopathy

In addition, the coagulation disturbances induced by a low temperature may have a much greater adverse effect after a severe head trauma with contusion bleedings than after a general transient non-traumatic hypoxia. It is well known that a body temperature just a few degrees below normal may induce coagulation disturbances[36,37] with significant increase in bleeding

times, and this may result in an increased amount of free blood in the brain tissue. It is well known from subarachnoidal haemorrage patients that free blood in brain tissue may have severe adverse effects such as vasospasm, a volume-occupying effect and fever.

Effects on ICP

Brain oedema with raised ICP is more common after a TBI than after global cerebral ischaemia. This means that the variations in ICP will be greater after a TBI than after a global cerebral ischaemia, as ICP varies on the steeper part of the pressure-volume curve. A decrease or increase in intracranial blood volume in TBI patients after cooling and rewarming, respectively, may therefore result in a significant effect on ICP and the rewarming-related increase in ICP may be a clinical problem in patients close to brain stem herniation.

Local cooling of the traumatized brain

The question has been raised as to whether selective active cooling of the brain may be more effective, with fewer side effects, than cooling of the whole body.[38] There may be less infection-related problems and problems with coagulopathy, but it is not clear whether the stress response and its effects on circulation of the penumbra zone, as well as the increase in ICP during the rewarming period, would differ from the condition of global cooling. Techniques for local cooling of the brain in humans is at present not available for general clinical use. Our preliminary results from 2 patients exposed to selective brain cooling via the nasal-oral cavity showed a relatively effective lowering of whole body temperature, but the difference between body temperature and brain temperature was only 0.1° C.

Conclusion

The present review summarizes the actual status of the clinical use of hypothermia in TBI patients and gives some tentative explanations as to why hypothermia has not been shown to be effective in improving outcome in these patients. We suggest that a stress-induced compromised circulation of the penumbra zone triggered by the difference between body and thermostat temperature, a more frequent use of vasoconstrictors under hypothermia, the risk of increased bleeding in contusions due to hypothermia-induced coagulation disturbances, and an increase in ICP following rewarming from a right- shifted intracranial pressure-volume curve, may adversely influence outcome. Currently, there is no scientific evidence for the use of active cooling in TBI patients. We believe that normothermia is to be preferred, and recommend that high fever should at first hand be treated by affecting the thermostat pharmacologically.[26]

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