# Can controlled therapeutic hypothermia act as a neuroprotective in severely head-injured patients?

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*A number of clinical trials have looked at the application of controlled therapeutic hypothermia as a neuroprotective in traumatic brain injury (TBI) with conflicting results. However, there is growing evidence that hypothermia can be used to great benefit in some patients with TBI warranting further investigation in this field.*

The concept of 'neuroprotection' by hypothermia dates back to ancient times, with the observation that infants abandoned and exposed to cold often remained viable for prolonged periods. The same applies to medical application of hypothermia, which has been described by the ancient Egyptians, Greeks and Romans.

The first clinical observations regarding hypothermia date from the 1930s and 1940s, with case reports describing successful resuscitation of drowning victims who were hypothermic, even after prolonged periods of asphyxia. The first case series describing its clinical application in patients with severe TBI was published in 1945.[1] Hypothermia was subsequently used in a number of clinical trials, all uncontrolled with varying treatment protocols and variable duration of hypothermia.[1–6] Although benefits were observed in some of these studies, these were variable and uncertain; experiments were discontinued because of severe side effects, management problems and uncertain benefits.[5,6] It should be noted that relatively deep hypothermia (28–30°C) was used in many of these studies.

In the 1980s interest in therapeutic hypothermia was rekindled by the positive results of a large number of animal experiments,[7–15] which showed that benefits could be obtained with mild (32–34°C) rather than moderate or deep hypothermia, with fewer, as well as less severe, side effects. Moreover, with the improvement of intensive care capabilities these side effects had become more manageable. This led to the initiation of clinical trials in various categories of patients. However, while recent clinical trials have unequivocally demonstrated improved neurological outcome in patients with post anoxic injury,[16,17] trials in patients with TBI have produced conflicting results.[18–30]

## NEUROPROTECTIVE EFFECTS OF HYPOTHERMIA – POSSIBLE MECHANISMS

Traditionally it has been assumed that protective effects of hypothermia were due to the slowing of cerebral metabolism, with an associated decrease in glucose and oxygen requirements. Indeed, cerebral metabolism is reduced by between 5% and 7% for each °C reduction in body temperature during moderate therapeutic hypothermia.[31,32] However, in animal experiments hypothermia's protective effects are greater than can be explained by reduced metabolism alone. Moreover, hypothermia appears to be effective even if initiated some time after injury, something that is difficult to explain by the above-mentioned mechanism alone. In recent years the destructive processes occurring in neural cells after ischaemia and other types of injury, and possible effects of hypothermia in these processes, have been partly elucidated. The data from animal models are to some extent supported by clinical studies and observations in humans.

These processes, which take place over a period of minutes to many days after injury, include:

- *Apoptosis.* Cells exposed to ischaemia can recover, become necrotic, or enter a path leading to programmed cell death, so-called apoptosis. There is a large body of evidence suggesting that hypothermia can prevent cell injury from leading to apoptosis via a number of different mechanisms.[33,34] Apoptosis develops over a relatively prolonged period (48 hours or longer), which may partly explain why hypothermia exerts protective effects even if initiated some time after injury.
- *Disturbances of ion homeostasis.* A period of ischaemia leads to prolonged and excessive $Ca^{2+}$ influx into the cell, induced by accumulation of excitatory neurotransmitters such as glutamate [review: 8,35]. This initiates an excitotoxic cascade where neurons remain in a permanent state of hyperexcitability, culminating in additional injury and cell death. This cascade continues in the hours, or even days, after ischaemia and can be triggered or accelerated by reperfusion. Various studies have shown that hypothermia can improve ion homeostasis and block or slow the destructive neuroexitatory processes.
- *Immune response and inflammation.* Various pro-inflammatory and immunological responses take place following ischaemia-induced cell injury, especially during reperfusion. Animal experiments[36] and

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clinical studies[37] have shown that large quantities of pro-inflammatory mediators are released following neurological injury. These mediators stimulate an inflammatory response that can significantly increase the extent of neural cell damage. Hypothermia is able to block or mitigate these ischaemia-induced inflammatory reactions and suppress the release of pro-inflammatory cytokines.[36,37]

- *Altered membrane permeability.* Ischaemia and reperfusion directly modify the fluidity and integrity of cell membranes.[38] There is evidence showing direct protective effects of hypothermia on this process of membrane disintegration.[38]
- *Free radical production.* Various studies have shown that ischaemia-induced generation of free radicals is blocked by moderate hypothermia.[39,40]
- *Vascular permeability and oedema formation.* Ischaemia induces disruptions in the blood brain barrier, facilitating subsequent development of oedema. The importance of brain oedema in the development of neurological injury in patients with TBI is well recognised.[41] These disruptions of the blood brain barrier may be further increased by therapeutic interventions such as administration of mannitol.[42] Hypothermia appears to reduce vascular permeability and blood-brain barrier disruption, thereby decreasing oedema formation.[43]
- *Cerebral thermo-pooling.* Yet another potential protective mechanism is the prevention and/or reversion of pathophysiological changes such as cerebral thermo-pooling that can take place in the brain following neurological injury.[44] Thermo-pooling signifies the presence of areas in the brain with significantly higher temperatures than the measured core temperature and differences can be up to 2–3°C. There is strong evidence that hyperthermia significantly increases the risk, and extent, of neurological injury. Thus isolated brain areas with increased temperature may suffer greater damage than other areas with lower temperatures, an effect that can be prevented or reduced by hypothermia.
- *Mitigation of intracellular acidosis*. Acidosis is a factor that can powerfully stimulate many of the above mentioned destructive processes. While extra-cellular pH usually decreases slightly during induction of hypothermia, there is evidence that intracellular acidosis is reduced.[45]

Thus in theory the processes leading to secondary cell injury death can be influenced for a substantial period of time, lasting for 48–72 hours following ischaemia. This would allow a significant time window for therapeutic interventions, including hypothermia, with the goal of providing neuroprotection.

An important facet in treating TBI is the realisation that a substantial part of the neurological damage does not occur immediately (at the moment of impact), but develops only at later stages, during hospital admission.[41] One of the causes of secondary injury is swelling of the brain, which can result in a rise in intracranial pressure (ICP) and reductions in cerebral blood flow leading to additional damage to injured areas of the brain. Other mechanisms involved in secondary brain injury include reperfusion injury of injured areas, release of excitatory glutamids and other deleterious biochemical cascades discussed above. These processes can be exacerbated by brain oedema and increased ICP, leading to a vicious cycle of ever increasing brain injury. Much effort in the treatment of TBI has focussed on the prevention or mitigation of this secondary injury.[41]

In theory, all of the above-mentioned processes that play a key role in the occurrence of secondary brain injury can be moderated by hypothermia.

## CLINICAL TRIALS IN TBI

Hypothermia has been studied in a number of small clinical trials between 1945 and the early 1960s. These efforts were abandoned when benefits could not be conclusively demonstrated and because of difficulties involved in caring for hypothermic patients in the absence of intensive care facilities and adequate monitoring equipment. Two decades later the combination of positive results from animal experiments, new insights in the pathophysiology of neurological damage following TBI, and improvements in facilities to care for these patients, has led to the instigation of several new clinical trials.

Since the early 1990s the results of 13 clinical studies, involving a total number of 1,321 patients, have been published.[18–30] The end points of these studies were intracranial pressure,[18–29] neurological outcome,[19–28,30] and survival.[19–28,30] All reported that hypothermia was able to significantly reduce intracranial pressure in patients with intracranial hypertension.[18–29] However, results regarding benefits on neurological outcome and survival have been conflicting.

Eight studies dealing with this issue were published between 1993 and 2001.[18–25] These were all single centre studies carried out in specialised and experienced neurotrauma centres. These studies mostly reported favourable effects of artificial cooling on neurological outcome.[18–25] However, with one exception[23] these studies were relatively small, and benefits were not statistically significant except in subgroup analysis. Benefits from hypothermia were observed mainly in patients with a Glasgow coma scale (GCS) of 4–7 on admission.[23]

All these studies were carried out in patients

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with high ICP; a study by Shiozaki *et al*. in 91 patients with normal ICP, of whom 45 were treated with hypothermia, observed no benefits in survival or neurological outcome.[30] In all the other studies, intracranial hypertension (ICP >20 or 25 mmHg; normal value <15 mmHg) was used as inclusion criterion, and decreases in ICP were used as one of the measures of effectiveness.

In 2001 the results of a large multi-centre trial by Clifton and associates were published. This study included 392 patients in 11 centres, and observed no benefits in survival or neurological outcome although, as in previous studies, hypothermia was able to decrease ICP.[26] Indeed there were more 'days with complications' in patients treated with hypothermia. The only group that appeared to benefit from hypothermia were those patients with low temperature already present upon admission.[26] An accompanying editorial stated that hypothermia for TBI should now be considered 'a good idea proved ineffective'. These findings, contradicting the results of all previous single-centre trials, led to the discontinuation of the use of hypothermia in most neurotrauma centres worldwide.

However, the recent publication of two trials reporting highly favourable effects of hypothermia in patients following cardiopulmonary resuscitation (CPR)[16,17] has rekindled interest in the application of hypothermia in TBI. In addition, in the past year the results of two new clinical trials have been published, both of which reported significant benefits of hypothermia in patients with TBI on neurological outcome and survival.[27,28]

One of these studies was carried out in our own centre in the Netherlands.[27] In a group of 136 patients, there was a statistically significant benefit in both neurological outcome and survival in the hypothermia group.[27] These benefits were observed in spite of the fact that hypothermia was used only as an option of last resort, in patients in whom all other forms of therapy had failed. Similarly to previous observations[23] the largest effects were seen in patients with a GCS of 5 or 6 at admission. In this group of patients, the percentage of patients with good neurological outcome was 29% *vs*. 8% in controls. Mortality was 52% *vs*. 76%, respectively. In contrast to other studies, hypothermia was maintained for significantly longer time periods in our study. Discontinuation of cooling was guided by ICP, and hypothermia was maintained as long as ICP rose above 20 mmHg if hypothermia was discontinued. Thus average duration of hypothermia was 4.8 (range 2–14) days in our study. In addition core temperatures below 34°C were achieved relatively quickly, with an average time interval of 3.1 hours.

The other recently published study, by Zhi *et al*., was carried out in China and included 396 patients, making it the largest study published so far.[28] These authors also maintained hypothermia for prolonged periods of time, averaging 62.4 hours (range 1–7 days). The authors reported significant differences in outcome between the hypothermia group and controls: good outcome, 38.8% *vs*. 19.7%; moderate disability, 22.7% *vs*. 18.2%; death, 25.7% *vs*. 36.4% for hypothermia patients *vs*. controls, respectively.

So how can the discrepancy between all these single-centre trials and the multi-centre study by Clifton *et al*. be explained?

One problem affecting the Clifton study may have been that some of the participating centres had little previous experience in the use of therapeutic hypothermia, and treated relatively few patients in the course of the clinical trial. Indeed there was significant inter-centre variance between hospitals participating in this study, with results of hypothermia appearing to be more favourable in larger centres with experience in the use of therapeutic hypothermia.[46] Treatment of TBI is a complex undertaking; supportive treatments and therapeutic interventions may vary substantially even between similar hospitals in the same country. Side effects of cooling may, if left untreated, negate any potential benefits of this treatment.[47] For example, artificial cooling may induce hypovolaemia, severe electrolyte disorders, arrhythmias and hypotensive episodes.[25,47,48] Indeed, in the Clifton trial hypotensive episodes (defined as MAP ≤70 mmHg lasting for more than 2 hours in this study) occurred more frequently in the hypothermia group compared to controls (10% *vs*. 3%, respectively).[26] Bradycardia associated with hypotension for two or more consecutive hours occurred in 16% of the patients in the hypothermia group, *vs*. 4% in the normothermia group; no sub-analysis was performed excluding these patients. Of note, no information is provided regarding episodes of hypotension with duration of less than 2 hours.[26] As even brief episodes of hypotension or hypovolaemia may adversely affect outcome,[41,49,50] these and similar issues may have affected the results of this trial.

An additional potential confounder is the potential risk of electrolyte disorders induced by hypothermia, especially in patients with TBI.[25,48] Magnesium may be particularly important in this regard;[14,51,52] hypomagnesaemia has been linked to adverse outcome in clinical studies, and animal experiments have suggested that magnesium has neuroprotective effects in neurological injury.[14,51,52] Serum levels of Mg and other electrolytes are frequently low in patients with TBI at admission,[53] and induction of hypothermia may compound this problem.[25,48]

Another side effect of hypothermia is insulin resistance and a decrease in insulin levels that will lead to hyperglycaemia if left untreated. This is yet another potential confounder, as hyperglycaemia is associated with increased mortality while strict regulation of glucose levels decreases mortality and length of stay in the ICU.[54,55] No information regarding glucose levels

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**Table 1. Potential side effects of therapeutic hypothermia. Many of these effects can be prevented or the effects mitigated**

| Frequency/degree of risk | Effect |
|---|---|
| High risk | Coagulopathy: increased bleeding time, increased APTT/CT, impaired coagulation cascade thrombocytopenia, thrombocytopathia<br>Electrolyte disorders* (loss of K, Mg, P, Ca)<br>Hypovolaemia (due to increased diuresis/hypothermia induced diuresis)<br>Rise in serum amylase<br>Changes in drug effects & drug metabolism<br>Insulin resistance |
| Intermediate risk | Airway infections |
| Low risk | Manifest bleeding, severe coagulation disorders (possibly higher risk in trauma patients and/or patients who already have bleeding problems for other reasons; hypothermia-induced coagulopathy may increase extent and severity of bleeding in these cases)<br>Wound infections and slowed healing<br>Myocardial ischaemia |
| Rare | Manifest pancreatitis<br>Intracerebral bleeding |

* Depends on category of patients; higher risk in TBI and SAH, lower risk in post-anoxia/CPR.

and/or occurrence of hyperglycaemia is provided in the paper by Clifton *et al*.[26]

These and other potential side effects associated with hypothermia,[56] (see also Table 1), can adversely affect neurological outcome, thereby partially or completely negating any beneficial effects. This could have affected the results of the multi-centre trial, especially because smaller centres with less experience in using therapeutic hypothermia may have been less adept at controlling side effects.

Nevertheless, in spite of the potential problems in interpreting the results of the Clifton trial, the fact that consistent benefits could not be demonstrated highlight the difficulties that can be involved in the use of therapeutic hypothermia in patients with TBI. These patients are often less 'stable' than patients following CPR, and side effects of induced hypothermia are likely to have a significantly greater impact in these patients.

Finally, there are significant differences in the length of time during which hypothermia was applied between the different studies and also in the way, and speed, in which patients were re-warmed. Most of the studies report improvements in outcome induced by hypothermia cooled patients for significantly longer periods of time, usually guided by ICP, and using slower rates of re-warming than the Clifton study. In our study[27] ICP was used to guide re-warming also, with cooling being re-initiated if ICP rose during re-warming.

## CONCLUSION

Results from animal experiments overwhelmingly support the concept of a protective role for hypothermia in TBI. However, clinical trials have provided conflicting results.

Positive effects on neurological outcome and survival have been achieved in tertiary referral centres with extensive experience in use of therapeutic hypothermia, using ICP to guide depth and duration of hypothermia and applying strict protocols for overall treatment of TBI. Benefits have been observed mainly in patients with GCS 4–7 at admission. Hypothermia is clearly effective in controlling intracranial hypertension, and so far benefits have only been demonstrated in TBI patients with high ICP. In addition, duration of hypothermia and speed of re-warming may play a key role in the achievement of positive effects on outcome. Animal experiments have shown that positive effects of cooling are (partly) lost if duration of hypothermia is too short, or if the speed of re-warming is too high. Most studies reporting benefits of cooling in TBI cooled patients for longer several days, guided by ICP. TBI patients with mild hypothermia (33–36°C) at admission who are haemodynamically stable should not be actively re-warmed, as this subgroup benefited from hypothermia even in the otherwise negative Clifton study.

Use of therapeutic hypothermia in TBI requires ICU admission and monitoring, intubation and sedation. Induction of hypothermia induces a large number of physiological changes in the circulatory and respiratory systems, coagulation system, drug metabolism etc.[56] For successful use of hypothermia, awareness of these physiological and pathophysiological effects is of supreme importance. Great care should be taken to prevent side effects such as hypovolaemia, hypotension, hyperglycaemia and electrolyte disorders, especially in patients with TBI.

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