# Current status of cerebral protection with mild-to-moderate hypothermia after traumatic brain injury

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**Purpose of review**

The aim of this article is to review the current status of protective effects of mild-to-moderate hypothermia on traumatic brain injury.

**Recent findings**

More than 30 clinical studies have reported effects of therapeutic hypothermia on outcome of traumatic brain injury and cerebral ischemia. Only one clinical trial of short-term mild hypothermia did not show any effect in patients with severe traumatic brain injury. Long-term mild hypothermia may be useful for severe traumatic brain-injured patients.

**Summary**

Mild-to-moderate hypothermia plays a significant role in cerebral protection after traumatic brain injury.

**Keywords**

mild hypothermia, therapy, traumatic brain injury

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**Abbreviations**

**GCS** Glasgow Coma Scale
**ICP** intracranial pressure
**TBI** traumatic brain injury


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## Introduction

Mild-to-moderate hypothermia as a treatment of brain injury has been a major area of research during the last decade. Laboratory studies have shown that mild-to-moderate hypothermia (32–35°C) has significant protective effects, diminishes the degree of neural damage, reduces mortality and improves neurological outcome [1,2]. Whether mild hypothermia improves the outcome of patients with severe traumatic brain injury (TBI) is still under debate. In this paper, we would like to review the current status of protective effects of mild-to-moderate hypothermia on TBI.

## Clinical trials of mild hypothermia after traumatic brain injury

Since the 1990s, more than 30 clinical studies have reported effects of therapeutic hypothermia on outcome of TBI, as well as its secondary injury mechanisms and complications after TBI [3,4]. McIntyre and colleagues [4] report a systemic review of 12 trials of therapeutic hypothermia involving 1069 patients. The results demonstrate an overall beneficial effect of mild-to-moderate hypothermia in severe TBI, with a 19% relative reduction in the risk of death and a 22% relative reduction in the risk of poor neurological outcome compared with normothermia. Furthermore, the findings of this systemic review also suggest that patients with severe TBI may benefit most from a longer duration of cooling, that is, more than 48 h. In fact, beneficial effects on secondary injury mechanisms may have occurred in patients treated with mild or moderate hypothermia for longer than 48 h, despite the established risks of complications from prolonged moderate hypothermia [5].

Clifton and colleagues [6], however, report that treatment with short-term mild hypothermia (24–48 h) fails to demonstrate the beneficial effects on outcome after severe TBI in adults. Several important limitations in that trial were later identified [3]. For instance, although a cerebral perfusion pressure-targeted therapeutic protocol was used in the study, the means by which that therapeutic goal was achieved varied between centers and may have created an impossible challenge for the therapeutic hypothermia. Furthermore, the duration of mild hypothermia by Clifton *et al.* is only 48 h, which may have been too short to control brain edema and intracranial hypertension, because cerebral swelling and brain edema are often greatest later than 48 h after injury [5].

More recently, we performed a randomized study to compare the effect of long-term mild hypothermia versus short-term mild hypothermia on outcome of 215 severe TBI patients with cerebral contusion and intracranial hypertension [Glasgow Coma Scale (GCS) $\leq$8]. Two hundred and fifteen patients aged 18–45 years with an admission GCS score of 8 or less within 4 h after injury were admitted and randomly divided into two groups: long-term ($5 \pm 1.3$ days) mild hypothermia ($n = 108$) and short-term ($2 \pm 0.6$ days) mild hypothermia ($n = 107$). The criteria for inclusion in the trial were age 18–45 years, a nonpenetrating head injury, a GCS score of 3 to 8 after resuscitation, frontotemporoparietal contusion with midline shift more than 1 cm on computed tomography scan, and intracranial pressure (ICP) over 20 mmHg. Patients were excluded if they had a GCS score of 3 with unreactive pupils and no spontaneous breathing, a life-threatening injury to an organ other than the brain, a systolic blood pressure of less than 90 mmHg after resuscitation, oxygen saturation of less than 94% after resuscitation, pregnancy, or known preexisting medical conditions (e.g., severe heart disease), or if doctors were not able to initiate cooling within 4 h after injury. At 6-month follow-up, outcome assessed with the Glasgow Outcome Scale showed that 47 of 108 (43.5%) cases had a favorable outcome in the long-term mild hypothermia group versus only 31 of 107 (29%) in the short-term mild hypothermia group ($P < 0.05$). The ICP significantly rebounded after rewarming in the short-term mild hypothermia group, and was significantly higher than that of the long-term mild hypothermia ($P < 0.05$). The incidence of stress ulcer, epilepsy, pulmonary infection, and cardio-arrhythmia was not significantly different between the two groups ($P > 0.05$). Therefore, our data show that long-term mild hypothermia significantly improves the outcome of severe TBI patients with cerebral contusion and intracranial hypertension without significant complications compared to short-term mild hypothermia. Our clinical data strongly suggest that 5 days of cooling is more efficacious than 2 days of cooling when mild hypothermia is used to control refractory intracranial hypertension in patients with severe TBI. Furthermore, early rewarming may not be optimal and can lead to both rebound intracranial hypertension and poor long-term outcome, when mild-to-moderate hypothermia is used to control refractory intracranial hypertension in patients with severe TBI [7••].

## Therapeutic window of mild hypothermia on traumatic brain injury

What is the therapeutic window of mild hypothermia to be effective for TBI? Most clinical trials have suggested that the earlier that mild hypothermia is initiated, the more likely beneficial effects may be obtained. Clinical data further show that mild hypothermia within 6 h after injury may be effective [5]. Hypothermia is currently being induced by surface cooling with use of cooling blankets, which usually requires 4–8 h to get the target hypothermia temperature (33–35°C) [6,7••]. Bernard *et al.* [8] recently reported that cooling can be achieved more rapidly (2°C over 30 min) by intravenous administration of iced (4°C) crystalloid solution. This use of cold intravenous fluids may represent a logical strategy for future clinical trials for hypothermia in severe TBI.

## Depth of mild hypothermia on traumatic brain injury

What depth of hypothermia is required to be effective for TBI without major complications? In severe hypoxic-ischemic injury, animal models suggest that the optimum temperature is between 32 and 34°C. Clinical trials also show that 33–35°C, but not higher than 35°C significantly improves the outcome of severe TBI patients [9]. Our data show that 33–35°C markedly reduces mortality and morbidity [7••]. As the body temperature falls below 32°C, there is an increased risk of infection [9]. Most clinical trials have suggested that 32–35°C may be effective and not cause major complications [5,9].

## Duration of mild hypothermia on traumatic brain injury

What is the duration of hypothermia to be effective for TBI? Because intracranial hypertension and brain edema may persist for longer than 1 week in patients with severe TBI, its use in TBI may importantly differ from hypothermic treatment for patients with cardiac arrest. European and Australian randomized prospective clinical trials have found that relatively brief periods (24–48 h) of mild hypothermia significantly improve outcome [10,11]. Yet short-term cooling was not effective in the randomized prospective clinical trial of hypothermia in adults with severe TBI by Clifton [6], and was not as efficacious as more prolonged cooling in our recent clinical study [7••]. Why might prolonged cooling be needed in TBI to optimize outcome? Prior studies [12••] and our current work suggest that rebound intracranial hypertension often occurs with early but not with late rewarming. This is unlikely to occur in cardiac arrest for which intracranial hypertension and brain edema may not be important factors in such patients. Iida and colleagues [13] recently monitored the velocity of blood flow in the internal carotid arteries in 11 patients with severe head injury who were cooled within 6 h of injury to 32–35°C for 48–72 h. Three of them had evidence of cerebral hyperemia followed by an increase in ICP during rewarming. The hyperemia resolved and ICP decreased when the patients were cooled again with mannitol, and barbiturates. More recently, Adelson *et al.* [12••] also found that rebound ICP elevations in a hypothermia group compared with those in normothermia were noted for up to 10–12 h after rewarming if mild hypothermia was only kept for 24 or 48 h in 48 pediatric TBI patients.

In a summary of 12 clinical trials of hypothermia for treatment of severe TBI, McIntyre and colleagues [4] report that in nine of the studies when body temperature was allowed to rise after either 24 or 48 h (a time when cerebral swelling is often greatest) outcome of hypothermia was ineffective compared to the normothermia group. In three of the studies when hypothermia was continued until ICP stabilized (3–14 days), however, it significantly reduced mortality and morbidity.

## Conclusion

Clinical trials have shown that long-term mild hypothermia plays a significant role in cerebral protection in TBI, which may be useful to treat severe traumatic brain-injured patients.

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## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 224–225).

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