REVIEW ARTICLE

Brain temperature management in traumatic brain injury

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Summary After a primary traumatic brain injury (TBI), the secondary brain damage that results from ischemia and reperfusion cascades is rather complex. The benefits and the mechanisms of action in whole-body cooling and selective brain cooling after TBI have been well investigated in animal studies. Despite a significant number of positive reports, induced hypothermia is not recommended as standard care for TBI patients in clinical practice because of its uncertain results. Furthermore, some authors have recommended maintaining normothermia and avoiding hyperthermia, although a consensus regarding the effective use of hypothermia in TBI patients has not been well established. In this paper, we propose that brain hyperthermia can be avoided early by maintaining, for at least 72 hours, a temperature ranging from normothermia to mild hypothermia (36–37.5°C), which is accomplished by utilizing selective brain cooling on the craniectomy side with an ice bag or by implementing other cooling systems. This may be a promising strategy when treating patients with severe TBI. However, further prospective research is clearly indicated to delineate the risks and benefits associated with these new therapies.

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1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability among children and young adults. It has limited treatment options. TBI survivors often suffer from severe disturbances regarding cognitive ability, memory, and neurological deficits. An unfavorable outcome rate
continues to be reported as 30–90%, despite the use of aggressive treatment. These results occur because of complex mechanisms such as ischemia and reperfusion-induced secondary TBI (including vascular damage, metabolic disturbance, lipid peroxidation, inflammation, and apoptosis), leading ultimately to cell degeneration and death.4

Induced hypothermia is an accepted strategy that improves outcome following anoxic brain injury associated with cardiac arrest, and is a recommended guideline in the treatment of these patients in Europe and in North America. Furthermore, hypothermia is also considered beneficial with regard to neurological outcome after neonatal birth asphyxia; however, its effects on TBI remain uncertain.

In this review article, we review the results of recent studies on the effect of induced hypothermia on TBI patients. We will also discuss the mechanisms of action, clinical application, and further work that involves in particular selective brain cooling in TBI patients.

2. Hypothermia induced by whole-body cooling

In 1943, induced therapeutic hypothermia for TBI was first studied. The possible mechanisms of the neuron-protective effects of whole-body cooling are suppression of the initial increase in the levels of excitatory amino acids such as glutamate; reducing calcium influx; stabilizing the blood–brain barrier and limiting cerebral edema; reducing the production of lipid peroxidation products; and reducing superoxide anion production in neurons and vascular cells during cerebral ischemia. Whole-body cooling is no longer recommended as a standard of care for patients with severe TBI because the risk of mortality is not significantly different between patients treated by the hypothermia and patients treated by normothermia. However, Fox et al in a meta-analysis review indicate that induced hypothermia has a clinically and statistically significant benefit on mortality and functional outcome. They emphasize that the cooling duration is a major factor that affects prognosis. For patients with severe TBI [Glasgow Coma Scale (GCS) ≤ 8] in neuro-critical care, they therefore recommend early prophylactic hypothermia cooling to a range of 32–34°C for 72 hours and/or not rewarming until the intracranial pressure (ICP) had normalized for 24 hours. Sinclair et al also indicate that inducing hypothermia for a sufficiently long period of time (i.e., 2–5 days) and rewarming the patient slowly (1°C increase in temperature every 4 hours) could be effective with regard to intracranial hypertension and neurological outcome in patients with severe TBI. The discrepancies in these reports result from their use of different cooling systems, target temperatures, monitoring systems, cooling duration, and rewarming course. Table 1 summarizes the recent studies that discuss the induction of therapeutic hypothermia in TBI patients.

3. Hypothermia induced by selective brain cooling

The development of selective brain cooling is based on the concept of only cooling the damaged brain and preventing complications related to whole-body cooling. Whole-body cooling is well associated with severe shivering; the requirement for anesthesia; and the increased incidence of arterial hypotension, cardiac arrhythmias, tendency to hemorrhage, and pneumonia. For example, surface cooling with cooling blankets or skin pads has the negative effects of triggering dermal vasconstriction and shivering, both of which consequently increase ICP. Therefore, if hypothermia can be performed without inducing systemic complications and can effectively reduce the intracranial temperature, useful data for the future evolution of hypothemic therapy may be produced.

The mechanisms of selective brain cooling have been well studied by Chio et al in animal studies. Using retrograde jugular vein flushing with 4°C saline treatment in fluid percussion-induced TBI rats, they have found that selective cooling without interfering with body temperature may improve the neurological outcomes of TBI patients by reducing brain ischemia and damage markers; reducing brain nitrostatic and oxidative damage; attenuating reactive astrogliosis and microgliosis; decreasing infarction volume and neuronal apoptosis; and stimulating further angiogenesis and neurogenesis. These results provide significant evidence that selective brain cooling could be a promising strategy for clinical applications.

Methods of selective brain cooling in clinical practice include the use of a cooling helmet, intranasal air, and cooling cap with a neckband. The results in some studies failed to show significant differences in neurological outcome when using a cooling helmet or intranasal air. However, cooling to achieve a target temperature of 33–35°C for 72 hours by using a cooling cap with a neckband could significantly decrease the ICP and improve neurological outcome. In 2009, Forte et al suggested that mild brain hypothermia (33.6–37.6°C for a mean period of 61.7 hours) induced by regional ice bag cooling was effective in controlling ICP in patients who had previously undergone decompressive craniectomy (DC). These results support the hypothesis that the least invasive and most selective methods of hypothermia hold the greatest promise of becoming practical neuroprotective measures after a TBI.

Decompressive craniectomy has been historically considered a salvage procedure in severe TBI patients. We demonstrated that DC is an independent predictor associated with a poor outcome in patients with TBI, that the perioperative neurological status of patients who underwent DC is more severe than the status of craniotomy patients, and 63% of patients who underwent early DC had a poor outcome after 6 months of follow-up. In accordance with the suggestions of Forte et al and our clinical experience, we are inclined to think that local brain cooling with an ice bag on the scalp surface around the craniectomy lesion may be another choice for these TBI patients. Its advantages are that it is a noninvasive and more specific method for cooling the lesion area. However, its benefits need to be confirmed.

After an acute neurological injury, the human brain is generally at a higher temperature than the rest of the body. Dissociation (i.e., reversal) between the intracranial temperature (ICT) and systemic temperatures—defined as the status in which the rectal temperature (Tr) exceeds
the ICT—is a poor prognostic factor and an early sign of brain death.\textsuperscript{40,41} We have further found that between survivors and nonsurvivors there is a significant difference in the incidence of the reversal phenomenon \textsuperscript{36,42} It has already been demonstrated that \textsuperscript{e} normothermia \textsuperscript{\textit{C} and 35} \textsuperscript{\textit{C}} induced by using \textsuperscript{\textit{C}} is beneficial to TBI patients (Table 1). However, Puccio et al\textsuperscript{47} showed that normothermia \textsuperscript{36–36.5} C induced by using an intraventricular cooling method proved to be equivalent to the ICT.\textsuperscript{39} We believe that the reduced ICT may be result of a concomitant decrease in regional cerebral blood flow and diminished cerebral metabolism. Based on our basic research and clinical findings, we want to emphasize that the optimal brain temperature and monitoring the condition of the brain need to be clarified for performing selective brain cooling as a strategy for artificially reversing the ICT-Tr gradient.

The sites at which temperature is measured include the rectum,\textsuperscript{18,19,21} urinary bladder,\textsuperscript{21,23} esophagus\textsuperscript{43} and brain.\textsuperscript{20,22,32–36,42} It has already been demonstrated that the ICT is normally \textit{0.5–1} C higher than the rectal temperature.\textsuperscript{39,42,45} These results remind us that the body temperature observed in different regions does not actually reflect the ICT. If a highly accurate ICT measurement is required, brain temperature monitoring should act as a guide for therapeutic interventions in patients with TBI, and serve as a control for cooling until the desired temperature is reached. Because the temperature gradient can apparently be as much as \textit{0.9} C from the cortex to the central brain,\textsuperscript{46} the uneven distribution of cooling of various brain regions should be a concern if selective brain cooling is performed. How to provide a uniform or an acceptable temperature gradient in different brain regions needs to be investigated in the future.

Selecting an ideal strategy in the rewarming phase is another important issue. In the rewarming phase, the most feared complication is an increase in the ICP.\textsuperscript{15} Most investigators suggest varying the speed of rewarming between \textit{0.5} C every 3 hours and \textit{1.0} C every day to avoid an abrupt elevation of brain temperature that subsequently induces increased ICP.\textsuperscript{18–22} To avoid an abrupt elevation of brain temperature, Forte et al\textsuperscript{36} advocated gradual and passive rewarming of the brain, with the intermittent application of ice packs to the area of the craniectomy. After a TBI, only one-third of patients achieve their highest ICP within the first 2 days after the injury, and \textit{20%} do not achieve their peak ICP until after 5 days.\textsuperscript{44} This is the reason why some authors recommend cooling to be extended to at least \textit{72} hours to avoid having a period of significant cerebral edema and elevated ICP (Table 1).

### 4. Normothermia induced by selective brain cooling

In most review articles, the authors suggest that a target temperature of hypothermia between \textit{32} C and \textit{35} C is beneficial to TBI patients (Table 1). However, Puccio et al\textsuperscript{47} showed that normothermia \textsuperscript{36–36.5} C induced by using an intraventricular cooling method proved to be equivalent

### Table 1 Comparison of various methods of hypothermia.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Number of patients</th>
<th>Method</th>
<th>Monitor</th>
<th>Target temperature (\degree C)</th>
<th>Duration</th>
<th>Rewarming rate</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marion\textsuperscript{18}</td>
<td>1997</td>
<td>82</td>
<td>Whole body</td>
<td>Rectal</td>
<td>32–33</td>
<td>24 h</td>
<td>No greater than \textit{1} C/h</td>
<td>No improvement</td>
</tr>
<tr>
<td>Jiang\textsuperscript{19}</td>
<td>2000</td>
<td>87</td>
<td>Whole body</td>
<td>Rectal</td>
<td>33–35</td>
<td>3–14 d</td>
<td>No greater than \textit{1} C/h</td>
<td>Improved GOS</td>
</tr>
<tr>
<td>Shiozaki\textsuperscript{20}</td>
<td>2001</td>
<td>91</td>
<td>Whole body</td>
<td>Brain urinary bladder</td>
<td>33.5–34.5</td>
<td>48 h</td>
<td>\textit{1} C/d</td>
<td>Improved GOS</td>
</tr>
<tr>
<td>Clifton\textsuperscript{21}</td>
<td>2001</td>
<td>392</td>
<td>Whole body</td>
<td>Brain urinary bladder</td>
<td>33</td>
<td>48 h</td>
<td>\textit{0.5} C/2 h</td>
<td>No improvement</td>
</tr>
<tr>
<td>Zhi\textsuperscript{22}</td>
<td>2002</td>
<td>396</td>
<td>Whole body</td>
<td>Brain urinary bladder</td>
<td>32.0–35.0</td>
<td>1 to 7 d</td>
<td>\textit{1} C/4 h</td>
<td>Improved GOS</td>
</tr>
<tr>
<td>Smrcka\textsuperscript{23}</td>
<td>2005</td>
<td>72</td>
<td>Whole body</td>
<td>Brain urinary bladder</td>
<td>33</td>
<td>48 h</td>
<td>\textit{0.5} C/2 h</td>
<td>No improvement</td>
</tr>
<tr>
<td>Clifton\textsuperscript{24}</td>
<td>2011</td>
<td>52</td>
<td>Whole body</td>
<td>Brain</td>
<td>—</td>
<td>12 h</td>
<td>Passive rewarming</td>
<td>No improvement</td>
</tr>
<tr>
<td>Andrews\textsuperscript{33}</td>
<td>2005</td>
<td>15</td>
<td>Intranasal cooling</td>
<td>Brain</td>
<td>33–35</td>
<td>72 h</td>
<td>Passive rewarming</td>
<td>Improved GOS</td>
</tr>
<tr>
<td>Qu\textsuperscript{34}</td>
<td>2006</td>
<td>90</td>
<td>Cooling cap + neckband</td>
<td>Brain</td>
<td>33–35</td>
<td>72 h</td>
<td>Passive rewarming</td>
<td>Improved GOS</td>
</tr>
<tr>
<td>Liu\textsuperscript{35}</td>
<td>2006</td>
<td>66</td>
<td>Cooling cap + neckband</td>
<td>Brain</td>
<td>33–35</td>
<td>72 h</td>
<td>Passive rewarming</td>
<td>Improved GOS</td>
</tr>
<tr>
<td>Harris\textsuperscript{32}</td>
<td>2009</td>
<td>25</td>
<td>Cooling cap craniectomy site ice bag</td>
<td>Brain</td>
<td>33</td>
<td>48 h</td>
<td>\textit{0.5} C/3 h</td>
<td>No improvement</td>
</tr>
<tr>
<td>Forte\textsuperscript{36}</td>
<td>2009</td>
<td>23</td>
<td>Cooling cap intracranial cooling</td>
<td>Brain</td>
<td>35.2</td>
<td>71.7 h</td>
<td>\textit{1} C/4 h</td>
<td>Decreased ICP</td>
</tr>
<tr>
<td>Puccio\textsuperscript{47}</td>
<td>2009</td>
<td>21</td>
<td>Intracranial cooling</td>
<td>Brain</td>
<td>36–36.5</td>
<td>72 h</td>
<td>Passive rewarming</td>
<td>Decreased ICP</td>
</tr>
</tbody>
</table>

\textit{GOS} = Glasgow Outcome Scale; ICP = Intracranial pressure.
to hypothermia in therapeutic efficacy. This method decreased the ICP and increased cerebral perfusion pressure. They emphasize that TBI in patients with multiple traumas limits the body surface area available for surface cooling. A drawback of this study is a target brain temperature ranging from 36°C to 36.5°C is not really normothermia, but in fact mild hypothermia. However, the definition of the terms "mild hypothermia", "moderate hypothermia", and "normothermia" is not precise at present. Another drawback is the lack of neurological outcome evaluation. Both of these drawbacks need to be clearly defined and investigated in the future.

5. Maintaining normothermia and avoiding hyperthermia

Brain hyperthermia is frequently seen in patients after a TBI. We have demonstrated that the frequency of brain hyperthermia was 17.7% and the mortality rate was 18% when maintaining brain normothermia (mean temperature of 37.3°C) to avoid hyperthermia (i.e., a brain temperature greater than 38°C) for 4 days in patients with severe TBI. The effect of hypothermia on TBI patients is uncertain and no consensus exists for the use of hypothermia in the treatment of patients following TBI. Farag et al. have therefore recommended maintaining normothermia and avoiding hyperthermia in TBI patients. Methods of determining optimal brain temperature management in TBI patients need to be investigated.

6. Conclusions

The benefits and the mechanisms of actions involved in inducing therapeutic hypothermia after TBI have been well established in animal studies. In clinical practice, however, the optimal brain temperature, type of cooling device, and strategy for the rewarming phase still need to be clarified. Since there is no apparent consensus regarding the use of hypothermia in TBI patients, we believe that at least maintaining normothermia and avoiding hyperthermia are useful in patients with TBI. We also believe that avoiding brain hyperthermia by early induced hypothermia by selective brain cooling at the craniectomy region with an ice bag or other cooling system or maintaining the temperate at normothermia to mild hypothermia (36–37.5°C) for at least 72 hours may in fact be a promising strategy for severe TBI patients. However, further prospective research is clearly indicated to delineate the risks and benefits associated with these new modes of therapy.

References


