Contemporary Management of Traumatic Intracranial Hypertension: Is There a Role for Therapeutic Hypothermia?

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Abstract

Objective Intracranial hypertension (ICH) remains the single most difficult therapeutic challenge for the acute management of severe traumatic brain injury (TBI). We reviewed the published trials of therapeutic moderate hypothermia to determine its effect on ICH and compared its efficacy to other commonly used therapies for ICH.

Methods A PubMed database search was done using various combinations of the search terms “brain injury,” “therapeutic hypothermia,” “intracranial hypertension,” “barbiturates,” “mannitol,” “hypertonic saline,” “hyperventilation,” “decompressive craniectomy,” and “CSF drainage.”

Results We identified 11 prospective randomized clinical TBI trials comparing hypothermia vs. normothermia treatment for which intracranial pressure (ICP) data was provided, and 6 prospective cohort studies that provided ICP data before and during hypothermia treatment. In addition, we identified 37 clinical TBI studies of lumbar CSF drainage, mannitol, hyperventilation, barbiturates, hypertonic saline, and decompressive craniectomy that provided pre- and posttreatment ICP data. Hypothermia was at least as effective as the traditional therapies for ICH (hyperventilation, mannitol, and barbiturates), but was less effective than hypertonic saline, lumbar CSF drainage, and decompressive craniectomy. Ultimately, however, therapeutic hypothermia does appear to have a favorable risk/benefit profile.

Conclusion Therapeutic moderate hypothermia is as effective, or more effective, than most other treatments for ICH. If used for 2–3 days or less there is no evidence that it causes clinically significant adverse events. The lack of consistent evidence that hypothermia improves long-term neurologic outcome should not preclude consideration of its use for the primary treatment of ICH since no other ICP therapy is held to this standard.

Keywords Brain swelling · Intracranial pressure · Therapeutic moderate hypothermia · Traumatic brain injury

Introduction

Brain swelling resulting in intracranial hypertension (ICH) occurs in the majority of patients with severe traumatic brain injury (TBI), defined as a postresuscitation GCS of 8 or less and an abnormal cranial CT scan. A retrospective evaluation of a large number of patients with severe TBI found that the worst swelling was during the first 3 days after injury in half of the patients [97], and ICH, defined as sustained intracranial pressures (ICPs) above 20–25 mm Hg, has been associated with poor outcomes [54]. Based on the assumption that the effective treatment of ICH will improve outcomes, the primary focus of contemporary neurotrauma critical care is the aggressive treatment of sustained ICPs >20–25 mm Hg, and avoidance of therapies that might cause or worsen ICH.

Therapeutic moderate hypothermia (cooling to 32–34°C) has been shown to improve functional and cognitive outcomes in murine and canine brain injury studies [10, 19, 67]. There is also experimental evidence that hypothermia is effective for reducing the edema associated with
intracerebral hemorrhage [41]. At least 11 prospective randomized clinical trials have evaluated the efficacy of therapeutic moderate hypothermia for severe TBI, but with conflicting results. Most of the single-center studies found a significant and positive treatment effect [11, 24, 38, 53, 68, 69, 87, 114], but none of the three multicenter studies did [12, 33, 88]. Because of the results of the larger multicenter trials, most clinicians no longer consider hypothermia for the treatment of patients with TBI. But hypothermia has been shown to be effective in reducing posttraumatic ICP elevations in virtually every published clinical trial, including the multicenter trials that found no long-term clinical benefit. Analysis of six studies that published ICP data before and after induction of hypothermia (32–34°C) for 367 patients with severe TBI revealed that ICP was decreased by an average of 10 mm Hg during the treatment [24, 38, 44, 57, 65, 77].

We undertook this review to better determine the appropriate place for moderate hypothermia in the therapeutic arsenal for posttraumatic ICH. Given the lack of improvement in long-term functional outcomes, we reviewed the evidence for short-term metabolic or physiologic effects that might explain the beneficial effect of hypothermia on brain swelling. In addition, we compared the efficacy of hypothermia with other contemporary, and newer, therapies for ICH.

Methods

A search of the MEDLINE PubMed database was performed on articles published between 1975 and 2008. Search terms included “brain injury,” “traumatic brain injury,” “intracranial hypertension,” “intracranial pressure,” and “ICP.” To these search terms, we added the terms “therapeutic hypothermia,” “moderate hypothermia,” “barbiturates,” “pentobarbital,” “mannitol,” “hypertonic saline,” “hyperventilation,” “decompressive craniectomy,” “CSF drainage,” or “lumbar CSF drainage.” From the results obtained with these searches, we selected articles that contained human data demonstrating the ICPs prior to and during the treatment period for inclusion in our review. All related Cochrane Database reports were cross-referenced to be sure all clinical trials of treatment of ICH were identified.

Results

Pathophysiologic Basis for Hypothermia Effect

Fever increases the cerebral metabolic rate by 10–13%/°C, and is a potent vasodilator [71]. Likewise, a reduction of body temperature from normal leads to a reduction of cerebral metabolism by an estimated 6.7%/°C, and corresponding decrease in blood flow [73]. Sahuquillo et al. have summarized our current understanding of the posttraumatic cellular and molecular adverse events that are highly temperature sensitive, and are thus good targets for therapeutic hypothermia [76]. They involve various degrees of ischemia, excitotoxicity, energy failure, neuronal death cascades, cerebral swelling, and inflammation. He reviews preclinical studies of ischemia and TBI which have found that hypothermia stabilizes the BBB and reduces posttraumatic levels of aspartate, glutamate, and hydroxyl radicals. Hypothermia also has been shown to decrease posttraumatic cerebral inflammation. Proinflammatory cytokines, and NO, are produced by activated microglia, and there is evidence that hypothermia suppresses the production of cytokines by microglia [56]. Hypothermia attenuates the posttraumatic elevation of levels of IL-1/βRNA, NGF, E-selectin, and ICAM-1, as well as suppressing neutrophil accumulation. Murine studies conclude that hypothermia potentiates the activation of the extracellular signal-regulated kinase (ERK)1/2 and the transcription factor cAMP response element-binding protein (CREB) after TBI [5].

In clinical studies there is evidence that hypothermia targets several different mechanisms of secondary brain injury. It has long been known to reduce functional metabolism, although probably does not significantly affect basal metabolism. This may explain why some studies of patients with severe TBI, where basal metabolism predominates, have not found a significant change in the cerebral metabolic rate of oxygen (CMRO₂) with hypothermia [53]. It is also consistent with the finding that hypothermia suppresses the evoked potential amplitudes in less severely injured, but not more severely injured, patients with severe TBI [113]. Others have observed as much as a 45% reduction in CMRO₂ associated with therapeutic hypothermia, although the reduction in metabolism is less pronounced after 24 h of treatment [57]. Hypothermia also can result in a significant reduction in anaerobic glycolysis (reduced lactate/pyruvate ratio) in brain tissue surrounding posttraumatic lesions [109].

The effect of hypothermia on global cerebral blood flow (CBF) is controversial. Metz et al. did not find a change in CBF as a result of hypothermia, or with rewarming, and concluded that the reduction in ICP associated with hypothermia was therefore not likely due to an effect on hyperemia or CBF [57]. However, Marion et al. found that hypothermia was associated with a significant reduction in CBF, with a mean of 28.8 ml/100 gr/min in the cooled group and 35.7 ml/100 gr/min in the normothermia group [53]. Shiozaki et al. documented a mean decrease of 15.4 ml/100 gr/min in CBF (from approximately 35 to 20 ml/100 gr/min) associated with cooling to 34°C [89]. In their study of 24 TBI patients with intact pressure
autoregulation, cooling to 34°C was not found to disrupt autoregulation, crudely determined as the response of ICP to changes in blood pressure. In that cohort, impairment of autoregulation was observed following rewarming if the brain temperature was allowed to exceed 37°C, however. A comparison of cerebrovascular reactivity of matched TBI patients not exposed to hypothermia suggested that a temperature-dependent hyperemic derangement of cerebrovascular reactivity was a phenomenon specifically related to therapeutic hypothermia used for refractory ICH [15]. In other words, the exposure to moderate hypothermia appeared to play an independent role in determining the vulnerability of cerebral vessels to rewarming in brain-injured patients.

Clinical Use of Hypothermia for ICH

The most dramatic and consistent clinical illustration of the efficacy of therapeutic hypothermia for ICH is acute liver failure. Approximately 20% of these patients die from brain swelling caused by elevated levels of ammonia and its metabolites, altered CBF, and elevated extracellular levels of glutamate and lactate [107]. In one cohort of 13 patients awaiting liver transplant, the ICP decreased from a mean of 36.5 to 16.3 mm Hg within 4 h after the patient was cooled to 32–33°C [37]. Hypothermia also has been found effective for several primary neurological disorders. In a recent randomized clinical trial of hypothermia for 24 h in children with severe TBI, the hypothermia group had a significant reduction in ICP at 16, 24, 48, and 72 h after injury compared to the normothermia group [33]. Several other studies of both adults and children with severe TBI have found a significant reduction of ICP with therapeutic hypothermia (Tables 1, 2). Moreover, a large meta-analysis of eight randomized controlled clinical trials of therapeutic hypothermia for severe TBI (748 patients) found that prolonged hypothermia was effective in reducing elevated intracranial pressure refractory to conventional therapies [30].

The failure of this beneficial effect on ICP to translate into improved functional outcomes in several multicenter trials may, in part at least, be due to rebound ICP elevations associated with rewarming that can be difficult to control [58]. Several cohort studies of stroke patients found that the rebound elevations of ICP associated with rewarming caused significant mortality [84, 85]. The association was perhaps most dramatically illustrated by a prospective study of 50 patients with complete middle cerebral artery occlusion who were treated with moderate hypothermia for 24–72 h [85]. During or shortly after rewarming, 15 of the 50 patients died as a result of a rebound increase in the ICP and associated herniation. To provide a more objective scientific approach to optimal timing for rewarming, Iida et al. investigated middle cerebral artery flow velocity with transcranial Doppler (TCD) in TBI patients who did or did not have acute brain swelling when they were rewarmed [35]. They found that TCD detection of hyperemia predicted acute brain swelling with rewarming, and advised that patients with this TCD finding should have longer periods of hypothermia and slower rates of rewarming.

Other therapies that effectively reduce elevated ICP, such as dexanabinol or hypertonic saline, also have been

Table 1: Randomized clinical trials of therapeutic mild-moderate hypothermia with normothermia control groups

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean ICP:H (mmHg)</th>
<th>Mean ICP:N (mmHg)</th>
<th>P value</th>
<th>Target temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelson et al. (P) [3]</td>
<td>35</td>
<td>14.86</td>
<td>17.48</td>
<td>&lt;0.05</td>
<td>32–33</td>
</tr>
<tr>
<td>Biswas et al. (P) [9]</td>
<td>21</td>
<td>9.5</td>
<td>12</td>
<td>N.S.*</td>
<td>32–34</td>
</tr>
<tr>
<td>Zhi et al. [114]</td>
<td>396</td>
<td>14–21.4</td>
<td>20.6–25.5</td>
<td>&lt;0.05</td>
<td>32–33</td>
</tr>
<tr>
<td>Clifton et al. [12]</td>
<td>392</td>
<td>15.65</td>
<td>17.4</td>
<td>N.S.**</td>
<td>33</td>
</tr>
<tr>
<td>Jiang et al. [38]</td>
<td>87</td>
<td>18.9</td>
<td>28.13</td>
<td>&lt;0.01</td>
<td>33–35</td>
</tr>
<tr>
<td>Marion et al. [53]</td>
<td>82</td>
<td>15.4</td>
<td>19.7</td>
<td>0.01</td>
<td>32–33</td>
</tr>
<tr>
<td>Qiu et al. [69]</td>
<td>80</td>
<td>22.5–24.7</td>
<td>24.6–25.9</td>
<td>0.003</td>
<td>33–35</td>
</tr>
<tr>
<td>Liu et al. [50]a</td>
<td>45</td>
<td>27.75</td>
<td>33.08</td>
<td>&lt;0.05</td>
<td>33–35</td>
</tr>
<tr>
<td>Smrcka et al. [91]</td>
<td>38</td>
<td>10.81</td>
<td>18.88</td>
<td>&lt;0.0001</td>
<td>34</td>
</tr>
<tr>
<td>Shiozaki et al. [87]</td>
<td>33</td>
<td>15b</td>
<td>25.4b</td>
<td>&lt;0.01</td>
<td>34</td>
</tr>
</tbody>
</table>

H hypothermia, N normothermia, P pediatric

* There were significantly fewer ICPs > 21 mmHg in the hypothermia patients during the period of cooling than in the normothermia patients during that time

** Percent of hypothermia patients with ICPs > 30 mmHg was significantly lower than the percent of normothermia patients with ICPs that high, but only during the time when the hypothermia patients were being cooled

a Comparison of selective brain cooling group with normothermia group, excluding systemic cooling group

b Estimates based on graphed data

* * *
found not to improve functional outcomes following TBI [8]. However, the most important effect of ICH, particularly if sustained and refractory to treatment, is brain death. This is a simple hemodynamic phenomenon, with intracranial pressure near to or greater than the blood pressure, resulting in a cerebral perfusion pressure inadequate to sustain cerebral metabolism. It may be that a reduction in ICP early after injury should not be expected to alter functional outcomes. In this regard, data from the TCDB found no correlation with ICP and memory functioning at 1 year after severe TBI [46].

Medical Complications Associated with Therapeutic Moderate Hypothermia

The potential for hypothermia to disrupt normal blood coagulation is of particular concern for trauma patients who may be at risk for intraabdominal or intracranial hemorrhage because of contused or lacerated tissues. Cooling below 30°C has been associated with bleeding diathesis and impaired liver function [4]. Kettner et al. carefully evaluated the effect of moderate hypothermia (32°C) in 16 anesthetized elective intracranial surgery patients [42]. During several hours of hypothermia, there was no change in the aPTT or Hct, and only a small and clinically insignificant change in the PT and platelet count was observed. Others have not found clinically significant hemorrhagic complications with the use of moderate hypothermia in patients with severe TBI [72].

Hypothermia also has systemic effects that have implications for the acute medical management of the cooled patient. Cooling suppresses the inflammatory response and leaves the patient at greater risk for infections, particularly with prolonged cooling for several days or more. Induced hypothermia has been shown to reduce leukocyte expression of heat shock protein 60, which is thought to be important in innate immune responses and may help explain the increased infection risk [28]. In addition, rapid cooling is well known to cause hypokalemia due to redistribution of potassium into the tissues. But whole body potassium levels usually do not change, and aggressive replacement of serum potassium should be avoided because it may result in hyperkalemia with rewarming [94]. None of the hypothermia clinical trials reported clinically significant cardiac or other complications as a result of hypothermia-induced hypokalemia. Hyperthermia decreases the systemic clearance of cytochrome P450-metabolized drugs between approximately 7 and 22%/°C below 37°C [105]. For example, a 2°C reduction of body temperature can double the duration of pharmacologic neuromuscular blockade [29]. In addition, cooling to 33°C has been associated with a significant prolongation of the latencies of all waves of both somatosensory-evoked potentials and brainstem auditory-evoked potentials, so the clinical interpretation of these studies must be modified to account for temperature [101].

Unlike accidental hypothermia, which results in significant physiological stress and depletion of high-energy phosphate stores, therapeutic hypothermia is usually accomplished with the pharmacologic induction of poikilothermia and prevention of shivering, and actually results in preservation of ATP stores [31].

Comparison of Hypothermia to Other Treatment Modalities

Conventional therapy for ICH has included hyperventilation, osmotic diuretics, ventricular CSF drainage, barbiturate coma, less severe sedation, and pharmacologic neuromuscular paralysis. More recently, hypertonic saline, lumbar CSF drainage, and decompressive craniectomy have been introduced. We found two or more systematic clinical studies of the effect of the treatment on ICP in TBI patients for hyperventilation, mannitol, barbiturate coma, hypertonic saline, lumbar CSF drainage, and decompressive craniectomy (Table 3, Fig. 1). In addition, we reviewed a clinical study of etomidate which observed an average of 12 mm Hg

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>During cooling (mean ICP, mmHg)</th>
<th>Before cooling (mean ICP, mmHg)</th>
<th>P value</th>
<th>Target temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al. [39]</td>
<td>215</td>
<td>18–20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28–29&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.05</td>
<td>33–35</td>
</tr>
<tr>
<td>Polderman et al. [65]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>64</td>
<td>14</td>
<td>37</td>
<td>&lt;0.01</td>
<td>32–34</td>
</tr>
<tr>
<td>Gal et al. [24]</td>
<td>30</td>
<td>12</td>
<td>18</td>
<td>0.0007</td>
<td>34.5</td>
</tr>
<tr>
<td>Lavinio et al. [44]</td>
<td>24</td>
<td>18.3</td>
<td>23.1</td>
<td>&lt;0.05</td>
<td>34</td>
</tr>
<tr>
<td>Metz et al. [57]</td>
<td>10</td>
<td>14.5</td>
<td>24</td>
<td>&lt;0.01</td>
<td>32.5–33</td>
</tr>
<tr>
<td>Sahuquillo and Vilalta [77]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23</td>
<td>16.8</td>
<td>23.8</td>
<td>&lt;0.001</td>
<td>32.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimates based on graphed data

<sup>b</sup> The subgroup of 64 patients with severe TBI that had intracranial hypertension refractory to barbiturate coma

<sup>c</sup> Pretreatment with intravenous infusion of cold saline at 4°C
reduction in ICP related to the treatment of three TBI subjects [48].

**Hyperventilation**

Hyperventilation has been used to treat ICH for nearly half a century and causes at least a temporary reduction in ICP because of a decrease in CBF and an associated reduction in CBV [52]. In five clinical studies (126 patients) that systematically evaluated the effect of hyperventilation on ICP, there was a mean decrease of 6.08 ± 4.22 (mean ± standard deviation) mm Hg [18, 23, 36, 93, 95]. But prolonged hyperventilation therapy is usually futile because the vasoconstrictive effect lasts <20 h, after which the pH of the CSF equilibrates with that of the blood and the cerebral vessels dilate [71]. More importantly, there is concern that the vasoconstriction from hyperventilation could cause or exacerbate ischemia in the injured brain. Investigators have observed a decrease in local CBF, an increase in cerebral O₂ extraction, worsening of cerebral O₂ metabolism, and a significant increase in the volume of critically hypoperfused brain tissue as a consequence of hyperventilation [14, 93]. Because of the effects on CBF and metabolism, current recommendations are that hyperventilation should be restricted to short-term use, such as emergency situations where a rapid decrease in ICP may be life-saving.

**Mannitol**

Mannitol is the most commonly used osmotic diuretic for the treatment of ICH [71, 92]. Nine clinical studies have systematically evaluated the effect of mannitol on ICH, and the average reduction after treatment in 140 patients was 7.93 ± 5.34 mm Hg [6, 23, 26, 34, 49, 78, 92, 93, 110]. A reduction of ICP can occur within 5 min after the administration of mannitol, although the peak effect is usually at 20–60 min and typically lasts for 1–6 h [43]. Mannitol causes intravascular expansion by osmotically drawing free water from the tissues (including the brain) into the plasma, resulting in a decrease in blood viscosity and improved cerebral perfusion. If cerebral autoregulation is intact, these hemodynamic changes result in vasoconstriction and a decrease in CBV and ICP [59]. There also is evidence that mannitol may decrease CSF production, which would

**Table 3** Comparison of contemporary therapies for intracranial hypertension

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total number of patients</th>
<th>Average decrease in ICP</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>126</td>
<td>6.08</td>
<td>4.22</td>
</tr>
<tr>
<td>Mannitol</td>
<td>140</td>
<td>7.93</td>
<td>5.34</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>167</td>
<td>8.47</td>
<td>6.71</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>367</td>
<td>9.97</td>
<td>6.66</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>133</td>
<td>15.06</td>
<td>7.34</td>
</tr>
<tr>
<td>CSF drainage</td>
<td>72</td>
<td>15.45</td>
<td>4.67</td>
</tr>
<tr>
<td>Decompressive craniectomy</td>
<td>192</td>
<td>19.15</td>
<td>7.70</td>
</tr>
</tbody>
</table>

**Fig. 1** Comparison of contemporary therapies for ICH
further decrease the ICP [66]. Because mannitol is a potent diuretic, aggressive fluid replacement is usually required with its use to maintain a normal intravascular volume. Abrupt discontinuation after prolonged use can result in a rebound increase in ICP, likely related to accumulation of mannitol in damaged brain and a reversed osmotic gradient [63, 92].

**High-Dose Barbiturates (Pentobarbital)**

The mechanism by which barbiturates decrease ICP is not precisely known, but it is believed to be due to a decrease in both CBF and CMRO₂ [61]. One study postulated that barbiturates work by reversing “dysautoregulation” and therefore improving cerebral oxygenation [100]. It has also been suggested that barbiturates have a neuroprotective effect at the cellular level [21, 55]. We reviewed three clinical trials that reported the use of high-dose pentobarbital to treat ICH in 167 patients, and the average decrease in ICP was 8.47 ± 6.71 mm Hg [16, 48, 100]. Barbiturates are currently considered “second tier” therapy for ICH because of a significant risk for severe hypotension [16, 64, 79].

**Hypertonic Saline**

Hypertonic saline (HTS) is increasingly being used to treat ICH, and causes a reduction in ICP through many of the same mechanisms as mannitol. Various saline concentrations, from 3 to 23.4%, have been used [71]. Like mannitol, HTS causes intravascular expansion by osmotically drawing free water from the tissues into the plasma, thus resulting in a decrease in blood viscosity and improved cerebral perfusion. If cerebral autoregulation is intact, these hemodynamic changes result in vasoconstriction and a decrease in CBV and ICP [7, 25, 82, 86, 112]. Experimental studies also suggest beneficial antiinflammatory effects and enhancement of cerebral perfusion as a result of HTS treatment [13, 20, 86, 106]. Eight clinical studies (133 patients) have systematically reviewed the effect of HTS on ICP and found an average decrease of 15.06 ± 7.34 mm Hg [6, 22, 27, 32, 70, 80, 98, 110]. Moreover, one study compared HTS to mannitol and found that HTS has a longer lasting and greater ICP-lowering effect [108]. The most common complications of HTS treatment are hypernatremia, complications associated with volume overload such as congestive heart failure, and, rarely, central pontine myelinolysis if a hyponatremic patient has a rapid increase in their serum sodium [81, 110–112].

**CSF Drainage (Lumbar)**

Until recently, lumbar drainage of CSF for the treatment of ICH was considered contraindicated in patients with severe TBI because it was thought to increase the risk for transtentorial or cerebellar tonsillar herniation. But there was no herniation observed in a series of 16 pediatric TBI patients who underwent lumbar CSF drainage for refractory ICH, and this route of CSF drainage has come to be accepted as a reasonable treatment alternative in selected patients [47]. Three studies reported the systematic evaluation of lumbar CSF drainage for posttraumatic ICH in 50 TBI patients, and found an average decrease of 15.45 ± 4.67 mm Hg [2, 60, 104]. The most common complication appears to be obstruction of the catheter. In addition, most only recommend this procedure for those with CT confirmation of the absence of large supratentorial mass lesions and with the presence of discernible basal cisterns [2, 60].

No studies were identified that provided before and after ICP data following ventricular CSF drainage, although one study of 22 patients with severe TBI did document an average ICP decrease of 8.6 mm Hg 20 min after drainage [23].

**Decompressive Craniectomy**

Decompressive craniectomy is a very aggressive means of treating ICH that has regained some popularity in recent years, particularly for younger patients with ICP elevations refractory to all other therapies [96]. Eight studies were reviewed in which before and after ICP data was provided for 192 patients who underwent decompressive craniectomy, and the average decrease in ICP was 19.15 ± 7.70 mm Hg [1, 40, 62, 74, 83, 90, 99, 102]. But complications associated with decompressive craniectomy also are the most serious, and include intracranial infection, infection of the bone flap, subdural or subgaleal hygroma, increased cerebral edema, hemorrhage, and hydrocephalus [1]. In addition, the patient will require a second operation for cranioplasty.

**Future Considerations for Therapeutic Hypothermia in TBI**

Some types of brain injury may respond better to therapeutic hypothermia than others [75]. Lescot et al. consider TBI as more like a syndrome than a disease, and suggest that the presence or absence of a large contusional volume will likely influence the efficacy of therapies used to reduce ICP [45]. For example, they suggest that osmotherapy, or CPP therapy, is not likely to be effective for patients with large contusions. They argue this not only based on their own clinical experience but also based on their observation that patients with large contusions typically have disruption of the blood–brain barrier and loss of autoregulation. Others have found that patients with severe diffuse swelling are not likely to respond to hypothermia, and in one
study of eight patients with very high ICPs (>40 mm Hg) and diffuse swelling, all eight died within 48 h of injury despite therapeutic hypothermia to 31°C [89]. Studies are needed to refine the pathophysiologic characterization of injuries with the use of serum or CSF biomarkers [51], and this should enable even better matching of injury type with effective treatments.

Moreover, it has been suggested that the duration of therapeutic hypothermia be flexible, and that it be used until ICP is under control regardless of how long that takes [17]. This notion is supported by a Chinese study of 215 patients with severe TBI that compared outcomes for those treated with hypothermia for 2 days with those cooled for an average of 5 days [39]. All patients had ICH, frontal contusions, and at least 1 mm of midline shift. In the 2-day cooled group they found that there was a significant rebound in the ICP associated with rewarming, but such rebound ICP increases were not seen in the 5-day (long-term) group. Six-month outcomes also were significantly better in the long-term hypothermia group compared with the 2-day group. But the reason several large clinical trials for TBI and other diseases have limited the duration of cooling to 12–48 h is that there is an increase in the incidence of infections and pulmonary complications associated with prolonged cooling.

The optimal target temperature for cooling is still not clear. Most agree that temperatures lower than 30°C should be avoided because of the increased risk of cardiac arrhythmias, coagulation abnormalities, and infection associated with moderate to severe hypothermia. More recently, Tokutomi et al. found that a consistent hypothermia-induced decline in elevated ICP was only seen when the temperature was reduced from 38 to 35°C, but not below that temperature, in a cohort of 42 patients with ICH and very severe TBI (GCS 3–5) [103]. Thus, if hypothermia is primarily used to treat elevated ICP, 35°C might be the optimal target temperature rather than 32–33°C.

In summary, hypothermia appears to be a good option to consider for patients with traumatic ICH. While there is research to be done to develop the optimal treatment regimen for hypothermia, the Class II–III studies to date support several recommendations:

- Intravascular cooling devices appear to allow for more rapid cooling, and the ability to better maintain the patient within a narrow target temperature range, than do conventional surface cooling techniques.
- The optimal target temperature may be 35°C rather than 32–33°C.
- The optimal duration of hypothermia is not known, and will likely vary among individual patients depending on the pathophysiology of the brain injury.
- Rewarming should be done slowly (e.g., over 12–24 h) so as to decrease the risk of rebound ICH. It is imperative to monitor ICP during rewarming.

**Conclusion**

Moderate hypothermia is an effective therapy for post-traumatic ICH with an acceptable side-effect profile, and should be considered as a primary treatment option for patients with severe TBI and elevated ICP. Clinicians should not refrain from its use solely because it has not consistently been shown to improve long-term neurologic outcomes; none of the other ICH therapies are held to this standard. In the future, various combinations of ICH therapies will likely be found to be more effective than the individual therapies alone, particularly for patients with varying types of brain injury due to the different anatomic and physiologic abnormalities associated with the various brain injuries as well as the distinct mechanisms through which the therapies exert their effects.

### References


