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Review

Therapeutic Hypothermia in Children and Adults with Severe Traumatic Brain Injury

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Great expectations have been raised about neuroprotection of therapeutic hypothermia in patients with traumatic brain injury (TBI) by analogy with its effects after heart arrest, neonatal asphyxia, and drowning in cold water. The aim of this study is to review our present knowledge of the effect of therapeutic hypothermia on outcome in children and adults with severe TBI. A literature search for relevant articles in English published from year 2000 up to December 2013 found 19 studies. No signs of improvement in outcome from hypothermia were seen in the five pediatric studies. Varied results were reported in 14 studies on adult patients, 2 of which reported a tendency of higher mortality and worse neurological outcome, 4 reported lower mortality, and 9 reported favorable neurological outcome with hypothermia. The quality of several trials was low. The best-performed randomized studies showed no improvement in outcome by hypothermia—some even indicated worse outcome. TBI patients may suffer from hypothermia-induced pulmonary and coagulation side effects, from side effects of vasopressors when re-establishing the hypothermia-induced lowered blood pressure, and from a rebound increase in intracranial pressure (ICP) during and after rewarming. The difference between body temperature and temperature set by the biological thermostat may cause stress-induced worsening of the circulation and oxygenation in injured areas of the brain. These mechanisms may counteract neuroprotective effects of therapeutic hypothermia. We conclude that we still lack scientific support as a first-tier therapy for the use of therapeutic hypothermia in TBI patients for both adults and children, but it may still be an option as a second-tier therapy for refractory intracranial hypertension.

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a major cause of death and disability in industrialized countries. In the United States, for example, an estimated 1.6 million people sustain TBI every year, with about 50,000 deaths and 80,000 permanent neurological disabilities (Ghajar, 2000). Several neuroprotective substances showing beneficial effects in animal studies, such as nimodipine, glutamate inhibitors, the competitive N-methyl-D-aspartate receptor antagonists, magnesium sulfate, and scavenging agents, have been analyzed in randomized trials in TBI patients, but none of these potential neuroprotective substances have been shown to be beneficial (Marshall, 2000; Narayan *et al.*, 2002; Maas *et al.*, 2006; Temkin *et al.*, 2007; Lu *et al.*, 2012). Modern therapy of TBI has improved outcomes over the last 20 years, but mortality and number of patients with severe disability have remained high (Patel *et al.*, 2005; Rosenfeld *et al.*, 2012; Gerber *et al.*, 2013).

Increased body temperature after a brain trauma is associated with increased cytokine release and worsening of outcome (Dietrich, 1992; Thompson *et al.*, 2003; Li and Jiang, 2012). Based on this and the neuroprotective effect of active hypothermia after global brain ischemia, such as after cardiac arrest (Bernard *et al.*, 2002; Hypothermia after Cardiac arrest Study Group, 2002) and after neonatal asphyxia (Shah *et al.*, 2007), and from case reports showing good recovery after drowning in cold water (Siebke *et al.*, 1975; Huckabee *et al.*, 1990; Husby *et al.*, 1990; Wanscher *et al.*, 2012), great expectations have been raised about active cooling as a breakthrough in TBI patients (Polderman, 2008). Hypothermia as a potential therapy after stroke is also under debate (Faridar *et al.*, 2011; Lakhan and Pamplona, 2012). Active cooling of patients with TBI was described first by Fay in 1945 and has become a major area of research during the last two decades (Fay, 1945). Spontaneous hypothermia, for example, as a consequence of progressive shock and inability to maintain normal temperature is, however, a poor prognostic factor (Finkelstein and Alam, 2010).

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There are several studies from the 1990s evaluating the effect of therapeutic hypothermia in severe TBI patients. Harris *et al.* (2002) reviewed seven randomized controlled trials from that period and found no beneficial effects of hypothermia on outcome. Another meta-analysis of eight randomized studies from the 1990s found no reduction in mortality from hypothermia (Henderson *et al.*, 2003). McIntyre *et al.* (2003) summarized the results of 12 studies from the 1990s, of which only 2 of the studies were graded high-quality studies. They concluded that the scientific support for therapeutic hypothermia so far is weak. In summary, the studies performed during the 1990s give no clear support for therapeutic hypothermia in TBI patients.

Hypothermia may still be beneficial by better planning of the studies and by optimizing the protocols as aimed at in later studies (McIntyre *et al.*, 2003). The purpose of this review was therefore to present and evaluate the current literature on therapeutic hypothermia in TBI patients from the year 2000 up to December 2013. We will also present possible side effects of active hypothermia based on the specific pathophysiology of these patients. The studies analyzed included patients who suffered a severe TBI (Glasgow Coma Scale [GCS] score ≤8) and a control group that was not exposed to active cooling.

Pathophysiology in TBI

The pathophysiology of brain injury after head trauma is complex and can be characterized by the initial primary injury and the subsequent secondary injury that develops over the days after the trauma. The primary injury occurs at the moment of impact and can be focal and/or more diffuse (Reilly, 2001; Werner and Engelhard, 2007; Harris *et al.*, 2009). The focal damage is seen as contusions, contusional bleedings, lacerations, intracranial hemorrhages, and local ischemia, and is an immediate effect of the trauma. The diffuse brain damage involves components such as neurons, neuronal processes, transmitter mechanisms, glial cells, blood vessels (Reilly, 2001; Werner and Engelhard, 2007), and diffuse brain swelling (Werner and Engelhard, 2007). It can also include diffuse axonal injury, which is a predictor of poor recovery (Greve and Zink, 2009; Smith *et al.*, 2013). Children suffer more severe edema after TBI than adults (Adelson, 2009).

The center of the primary brain injury is often severely hypoxic and more or less insensitive to therapeutic interventions, and most cells of these areas will die irrespective of therapy (Werner and Engelhard, 2007), while injured cells of the surrounding areas have greater potential to survive.

Secondary brain injury is initiated at the moment of injury with progression over the ensuing minutes, hours, and days (Marshall, 2000; Li *et al.*, 2012), a phenomenon termed hemorrhagic progression of a contusion (Kurland *et al.*, 2012). The development of secondary brain damage is a major factor determining the patient's clinical outcome (Reilly, 2001; Greve and Zink, 2009). A main target is therefore to reduce the development of secondary brain damage, by improving the survival of injured but not dead cells. The pathophysiological mechanisms behind the secondary damage are not fully understood. Acceleration, deceleration, and rotational forces of the brain may induce damage of axons and other brain cells. Overall effects of biomolecular and physiological changes in the injured brain, including neuroinflammatory processes with release of cytokines, excitotoxic substances, cerebral edema, increased ICP, and compromised cerebral blood flow with cerebral ischemia and apoptosis, may be involved (Marshall, 2000; Wagner *et al.*, 2004; Algattas and Huang, 2014). A specific goal with the use of neuroprotective substances has been to reduce the development of secondary injuries by reducing the direct toxic cell damage, and the cytotoxic brain edema. The pathophysiology, however, seems to be more complex, as neuroprotective substances tested so far in patients have failed to improve outcome. One can speculate that primary hypoxia, especially in and around contusions, may be an important additional triggering mechanism behind the pathophysiological alterations after a TBI. If so, one goal in the treatment of these patients should be to counteract the effects of hypoxia of the brain, e.g., by hypothermia.

TBI is supposed to increase the permeability of the tight cerebral capillaries (open the intact blood–brain barrier). Failure of the blood–brain barrier means that the normally impermeable capillaries become passively permeable to small solutes, which may cause leakage of fluid into brain tissue, a mechanism responsible for the so-called vasogenic brain edema (Grände, 2006; Chodobski *et al.*, 2011). Brain edema can also be an effect of swelling of brain cells, because of cell membrane damage from hypoxia, and cytotoxic and excitatory substances (Liang *et al.*, 2007). Brain edema and intracranial hematomas will increase ICP and reduce cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure and ICP. A high ICP correlates to worse outcome in patients with TBI (Jiang *et al.*, 2002) and is an important cause of death after severe TBI. Low CPP values, especially combined with hypovolemia, may cause brain ischemia in areas with compromised circulation (Greve and Zink, 2009).

Therapeutic Hypothermia in TBI

As mentioned in the Introduction, hypothermia has neuroprotective effects related to global hypoxia. This initiated the view that the neuroprotective effect of active hypothermia in combination with its ICP-reducing effect might be an important therapeutic option also in TBI patients (Biswas *et al.*, 2002; Polderman *et al.*, 2002; Tokutomi, 2009; Hutchison *et al.*, 2010).

Brain metabolism is reduced by about 5–7% per °C reduction in core temperature (Finkelstein and Alam, 2010). The ICP reduction by active hypothermia can be explained by cerebral vasoconstriction caused by reduced metabolic rate resulting in reduced intracranial blood volume. Reduction in brain metabolic rate may be one mechanism for neuroprotection by hypothermia, that is, by causing a more favorable balance between cerebral oxygen and glucose supply and demand (Oddo and Urbano, 2012). The same decrease in metabolic rate from barbiturate treatment was, however, not associated with improved outcome (Roberts and Sydenham, 2012). The effect of hypothermia is more complex than just a reduction in metabolic rate. Many posttraumatic adverse events at the cellular and molecular level are highly temperature sensitive (Sahuquillo and Vilalta, 2007). Protective factors by therapeutic hypothermia may also be attenuation of proinflammatory cytokines, decrease in free radicals, decrease in toxic metabolites and excitatory substances, prevention of reperfusion injury, prevention of apoptosis, preservation of high-energy phosphates, reduced mitochondrial dysfunction, and a reduction in oxidative stress (Dietrich, 1992; Wagner *et al*., 2004; Ji, 2007; Polderman, 2008; Bayir *et al.*, 2009; Li and Jiang, 2012). Posttraumatic hypothermia treatment has also been shown to attenuate the burden of axonal damage in rodent models of TBI (Smith *et al.*, 2013).

Cooling Technique and Protocol

Cooling of the whole body (systemic cooling) has been used in most larger clinical TBI outcome studies so far. Local cooling of the brain has been discussed to reduce systemic complications such as pulmonary complications and coagulation disturbances (Qiu *et al.*, 2006; Finkelstein and Alam, 2010; Shlee and Lyden, 2012). Selective brain cooling can be obtained by a cooling cap or by intranasal cooling with circulating cold water via a tubing/balloon system inserted into the nose (Springborg *et al.*, 2013). Local cooling, especially with an intranasal cooling technique, has difficulty in reaching target temperatures within reasonable times (Harris *et al.*, 2012; Springborg *et al.*, 2013). Liu *et al.* (2006) and Qiu *et al.* (2006) both succeeded in reducing the brain temperature to 33–35°C using a cooling cap in combination with an ice neck strap, and they reported positive results on outcome, and a lower risk of pneumonia compared with systemic hypothermia (Liu *et al.*, 2006). Additional technical developments are necessary before selective cooling of the brain can be used as a reliable technique (Harris *et al.*, 2012).

Systemic cooling can be obtained by surface cooling, most often with a cooling blanket (Polderman, 2004) or cooling with endovascular catheters (Shlee and Lyden, 2012). These techniques have the capacity to cool the whole body to the desired temperature within reasonable times. Hypothermia is classified as light or mild (>34°C), moderate (32–34°C), or severe (<32°C). The clinical studies reviewed in this study have used light to moderate hypothermia with a goal temperature of 33–35°C.

The degree of hypothermia is normally determined by the core temperature measured rectally, in the esophagus, or in the urinary bladder. Outcome in TBI when using active hypothermia may be related to how long after the accident the cooling began, the goal temperature, time to reach the goal temperature, and time period of cooling and rewarming (Finkelstein and Alam, 2010). For example, the negative effects of rewarming—that is, the rebound increase in ICP during the rewarming and postcooling phase—may overshadow the neuroprotective effects of cooling. Alternative protocols with a shorter time delay before the start of cooling after the accident, a more long-term cooling period, or an extended rewarming phase and better control of ICP and CPP might strengthen the beneficial effects of hypothermia (McIntyre *et al.*, 2003).

Evaluation of Outcome

Most studies used the five-category-assessment Glasgow Outcome Scale (GOS) to evaluate outcome: 1, death; 2, vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery. A GOS score of 4–5 is considered as a favorable/good neurological outcome, while a GOS score of 1–3 is unfavorable/poor outcome (Jennet *et al.*, 1981).

The Pediatric Cerebral Performance Category (PCPC) scale was used in 3 of the 5 pediatric trials. PCPC is a six-point scale: 1, normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, persistent vegetative state; 6, death (Biswas *et al.*, 2002; Hutchison *et al.*, 2008).

Cooling Duration and Rewarming

Most studies used a cooling period in the 24–48-hour range, while some studies have used a cooling period longer than 48 hours. One reason for using more long-term cooling is that cerebral swelling and edema often are greatest 3–5 days after injury (Fox *et al.*, 2010). If hypothermia is discontinued at an earlier stage, the injury mechanisms may continue to progress with a greater risk of rebound increase in ICP (Schwab *et al.*, 2001). A study by Jiang *et al.* (2006), who compared the effects of long-term cooling with short-term cooling in adults, indicated that longer duration was beneficial.

Cooling generally results in a decrease in ICP, both in adults and in children (Adelson *et al.*, 2005; Finkelstein and Alam, 2010). Only one study has shown an increase in ICP by cooling (Clifton *et al.*, 2011). As mentioned above, the recently started Eurotherm3235Trial (Andrews *et al.*, 2013) is based on the hypothesis that the ICP-reducing effect of hypothermia is favorable. A rebound increase in ICP during the rewarming period has been more common in studies using short-term cooling. A more slow and well-controlled rewarming (Povlishock and Wei, 2009) and better control of ICP, blood pressure, and CPP may reduce the adverse rebound effect of the rewarming phase.

Adverse Effects of Hypothermia

Even though cooling is neuroprotective and improves outcome after a general brain hypoxia as described in the Introduction, the situation may be different after TBI, which may affect the therapeutic effect of hypothermia. While cerebral circulation is relatively normal or may even be above normal after resuscitation after general hypoxia, the traumatized brain often suffers from compromised circulation and hypoxia in and around the most injured areas of the brain. The traumatized brain also suffers from specific trauma-induced inflammatory processes (Algattas and Huang, 2014).

Shivering, increased stress, and increased sympathetic discharge and catecholamine release are well-known effects of hypothermia with the physiological aim of resetting body temperature toward the values set in the biological thermostat of the brain. The hypothermia-induced reduction in metabolic rate will therefore be counteracted by a simultaneous stress-induced increase in metabolism (Badjatia *et al.*, 2008). The latter may increase oxygen demand and energy expenditure. It may also compromise brain microcirculation by an increase in release of catecholamines, which may aggravate hypoxia especially in areas in which the perfusion is already significantly reduced. Oddo *et al.* (2010) showed that cooling-induced shivering can cause a significant reduction in brain oxygenation with an increased risk of brain hypoxia. These authors warned against the use of active hypothermia as prophylactic neuroprotectant in the early phase of TBI (Oddo *et al.*, 2010; Urbano and Oddo, 2012). Shivering can be reduced pharmacologically, for example, by neuromuscular blocking agents, but this therapy has well-known side effects, that is, in terms of increased risk of pulmonary emboli, and the increased sympathetic discharge is maintained. Hypothermia is also associated with hypotension, pulmonary infections, thrombocytopenia, hypokalemia, and increased risk of bleedings caused by general coagulation disturbances (Rundgren and Engström, 2008; Finkelstein and Alam, 2010). Hypothermia may also trigger a reduction in plasma volume (Hammersborg *et al.*, 2005). It may also be clinically relevant that hypothermia reduces and rewarming increases the elimination rate of drugs (Empey *et al.*, 2013). Noradrenalin given to compensate for hypothermia-induced hypotension may be beneficial by preserving CPP, but it may also induce pulmonary complications (Contant *et al.*, 2001) and compromised cerebral circulation.

Trials Included and Outcome

We found 19 original articles that met the inclusion criteria, 14 of which included all ages or adult patients only, and 5 were pediatric. The characteristics of the trials are given in Table 1. Information about mortality and neurological outcome, complications, and ICP is presented in Table 2.

The studies by Clifton *et al.* (2001, 2011) can be classified as high-quality studies involving 392 and 97 patients, respectively. There were no significant difference in mortality between the hypothermia group and the normothermia group in these studies. However, the study from 2001 showed more frequent episodes of hypotension and low CPP with hypothermia therapy, and there was a longer hospital stay for patients in the hypothermia group in that study. In the study from 2011, noradrenalin was more commonly used to prevent hypotension. In spite of this and that the patients were younger in the hypothermia group, outcome was not better in the hypothermia group in that study. This study also showed a tendency of poorer outcome in patients with diffuse brain injury treated with hypothermia compared with the control group, but there was better outcome with hypothermia in the subgroup of patients who underwent surgical removal of intracranial hematomas.

The study by Harris *et al.* (2009) included 12 and 13 patients in the hypothermia and normothermia group, respectively. These authors investigated the effect of local hypothermia with a cooling cap, but they had difficulty in reaching the target temperature of 33°C for all patients. They did not find any difference in GOS or in complications between the groups.

Four of the studies in adult patients (Polderman *et al.*, 2002; Zhi *et al.*, 2003; Inamasu *et al.*, 2006; Liu *et al.*, 2006) showed lower mortality and more patients with favorable outcome in the hypothermia groups than in the control groups. The study by Liu *et al.* (2006) had 22 patients in each of the 3 groups: a hypothermia group with selective brain cooling, a hypothermia group with systemic cooling, and a normothermia group. The two hypothermia groups did not differ regarding outcome, but had better outcome than the control group. The randomized trial by Zhi *et al.* (2003) involved two groups with 198 patients per group and showed that hypothermia was beneficial for neurological outcome and mortality. In the trial by Polderman *et al.* (2002), the hypothermia group included 64 TBI patients with ICP higher than 20 mmHg in spite of standard treatment including barbiturate treatment. Hypothermia was continued until ICP remained at 20 mmHg or less for 24 hours. The control group consisted of 72 patients given a standard treatment including barbiturate treatment. This means that the two groups were not fully comparable. The study suffered from the highest mortality reported: 63% and 72% in the hypothermia group and the control group, respectively. The beneficial effects of hypothermia on mortality and outcome in that study were limited to the subgroup of patients with GCS of 5 or 6 at admission. Inamasu *et al.* (2006) evaluated the effect of hypothermia for patients with severe TBI (GCS ≤ 6) with acute subdural hematoma. They evaluated 18 patients with acute surgery and found improved survival and favorable outcome compared with a historic control group of 15 patients.

The trials by Qui *et al.* (2006), Lee *et al.* (2010), and Zhao *et al.* (2011) showed improved favorable neurological outcome with hypothermia, but no effect on mortality. The study by Zhao *et al.* (2011) had 40 patients in the hypothermia group and 41 patients in the normothermia group. Three months after treatment, more patients had favorable outcome in the hypothermia group ($p < 0.04$). The study by Qui *et al.* (2006) had 45 patients in each group. At 6 months after TBI, there was no difference in mortality between the groups, but there were more patients with favorable outcome in the hypothermia group. The study by Lee *et al.* (2010) was randomized, and involved three groups with patients with a GCS score of between 4 and 8. In group 1 ($n = 16$), the treatment was guided by ICP/CPP. In group 2 ($n = 15$), the treatment was also ICP/CPP guided, but included moderate hypothermia (33–35°C) as well. Group 3 ($n = 14$) was guided by measurement of brain tissue oxygen and included the same moderate hypothermia. Mortality was low in all groups, and did not differ between the groups. In another study by Qiu *et al.* (2007), the effect of hypothermia was analyzed in patients after craniotomy, with a hypothermic group and a normothermic group with 40 patients in each. In this randomized study, mortality was lower and favorable neurological outcome was better in the hypothermia group. In a study by Yan *et al.* (2010), the patients were divided into three groups according to GCS score (GCS 7–8, 5–6, and 3–4) and improved outcome by hypothermia was shown only in the group with GCS score 7–8. In a study by Gal *et al.* (2002) with 15 patients per group, there was a tendency of better outcome in the hypothermia group. A recent large retrospective multicenter study from Japan based on data from the Japan Neurotrauma Data Bank including 401 patients showed a tendency of higher mortality, but better favorable neurological outcome in surviving patients in the hypothermia group. The study can be criticized, however, as the patients in the hypothermia group were significantly younger, and inclusion criteria, such as age and method of temperature management, differed between the institutions (Suehiro *et al.*, 2014).

Three of the five pediatric studies analyzed reported that patients treated with hypothermia were slightly more prone to die (Biswas *et al.*, 2002; Hutchison *et al.*, 2008; Adelson *et al.*, 2013) and two showed no clear effect on mortality and neurological outcome by hypothermia (Adelson *et al.*, 2005; Li *et al.*, 2012). The study by Biswas *et al.* (2002) included only 21 patients, and the authors stated that no conclusion could be drawn from their study regarding outcome.

Special attention should be paid to the higher mortality rate with hypothermia in the properly designed pediatric study by

Table 1. Characteristics of Included Trials

Author (year)	*Study design*	*Population (n)*	*Age (years)*	*Therapy incl. time interval and temperature*	*Limitations/comments*
Suehiro *et al.* (2014)	Observational study	401	NR	Therapy and time interval NR. Temp <35°C in all clinical centers.	Multicenter study based on data from the Japan Neurotrauma Data Bank. Mean age significantly lower in hypothermia groups. The control and hypothermia groups not comparable. Outcomes assessed at discharge. No follow-up time.
Zhao *et al.* (2011)	RCT	81	>16	Systemic cooling to rectal temp 33°C for 72 hours. Spontaneously rewarmed.	Unclear randomization. Short follow-up time. Complications NR.
Clifton *et al.* (2011)	RCT	97	16–45	Systemic cooling to 33°C for 48 hours. Rewarmed by 0.5°C every 2 hours.	High-quality multicenter study. Did not include patients >45 years.
Yan *et al.* (2010)	RCT	148	18–64	Systemic cooling to rectal temp 32–34°C for 3–5 days. Spontaneously rewarmed.	Significance and *p*-values for mortality and outcome NR. Complications NR.
Lee *et al.* (2010)	RCT	45	12–70	Systemic cooling to brain temp 33–35°C.	Small sample size. Cooling duration and rewarming rate NR. All patients with GCS 3 were excluded.
Harris *et al.* (2009)	RCT	25	>18	Selective brain cooling to intracranial temp 33°C for 24 hours. Rewarmed by 0.5°C every 3 hours for 24 hours.	Small sample size. The target intracranial temp of 33°C was not maintained. Short follow-up time.
Qiu *et al.* (2007)	RCT	80	19–65	Systemic cooling to brain temp 33–35°C for 4 days. Spontaneously rewarmed to baseline.	All patients had a craniotomy before treatment. Significance and *p*-values for mortality NR.
Liu *et al.* (2006)	RCT	66	19–65	Local brain cooling group: brain temp 33–35°C for 72 hours. Systemic cooling group: rectal temp 33–35°C for 72 hours. Spontaneously rewarmed.	Small sample size.
Qui *et al.* (2006)	Prospective study	90	19–65	Selective brain cooling to brain temp 33–35°C for 72 hours. Spontaneous rewarming.	No randomization.
Inamasu *et al.* (2006)	Retrospective study	33	NR	Systemic cooling to brain temp 34–35°C for 3 days. Rewarmed 1°C/day.	Retrospective study with historical controls. Small sample size. Only patients with GCS ≤ 6. Two patients <18 years.

(*continued*)

Table 1. (Continued)

Author (year)	*Study design*	*Population* (n)	*Age (years)*	*Therapy incl. time interval and temperature*	*Limitations/comments*
Zhi *et al.* (2003)	RCT	396	15–65	Systemic cooling to rectal temp 32–33°C for 1–7 days. Rewarmed 1°C every 4 hours when ICP was normal for 24 hours.	Unclear randomization. Mean GCS was higher in the control group.
Gal *et al.* (2002)	Prospective study	30	NR	Systemic cooling to core temp 34°C for 72 hours. Slowly rewarmed (rate NR).	No randomization. Small sample size. No inclusion or exclusion criteria reported except GCS 3–8.
Polderman *et al.* (2002)	Prospective study	136	NR	Systemic cooling to 32°C until ICP remained ≤ 20 mmHg for 24 hours (24 hours to 21 days). Then rewarmed 1°C per 12 hours.	No randomization. The hypothermia and control groups not fully comparable.
Clifton *et al.* (2001)	RCT	392	16–65	Systemic cooling to bladder temp 33°C for 48 hours. Rewarming at maximum 0.5°C per 2-hour period.	Multicenter study.
Adelson *et al.* (2013)[a]	RCT	77	0–17	Systemic cooling to rectal or brain temp 32–33°C for 48–72 hours. Rewarmed 0.5–1°C every 12–24 hours.	Multicenter study. The study was terminated early after a futility analysis. Short follow-up time. Patients with GCS 3 were excluded.
Li *et al.* (2009)[a]	RCT	22	0.5–9	Selective brain cooling to intracranial temp 34.5 ± 0.2°C for 72 hours. Rewarming rate NR.	No long-term follow-up. Small sample size.
Hutchison *et al.* (2008)[a]	RCT	225	1–17	Systemic cooling to esophageal temp 32.5 ± 0.5°C for 24 hours. Rewarmed 0.5°C every 2 hours.	High-quality multicenter study. Patients with acute isolated epidural hematoma were excluded.
Adelson *et al.* (2005)[a]	RCT	75	0–17	Systemic cooling to rectal temp 32–33°C for 48 hours. Rewarmed 1°C every 3–4 hours.	One multicenter trial ($n=48$) and one parallel single-institution trial ($n=27$) with different inclusion criteria.
Biswas *et al.* (2002)[a]	RCT	21	0–17	Systemic cooling to rectal temp 32–34°C for 48 hours. Rewarming at maximum 1°C/hour.	Small sample size.

[a] Pediatric trial.

GCS, Glasgow Coma Scale; hypo, hypothermia; ICP, intracranial pressure; NR, not reported; RCT, randomized controlled trial; temp, temperature.

Hutchison *et al.* (2008) and the lack of any positive effects in the also well-designed recent pediatric study by Adelson *et al.* (2013). The latter showed no difference in neurological outcome between the hypothermia and the control group and there was a tendency of higher mortality rate ($p = 0.15$) in the hypothermia group. The study was terminated early after a futility analysis. This can be compared with the pediatric study by Adelson *et al.* (2005), which showed a tendency of reduced mortality with hypothermia treatment. The alternative protocol used by Adelson *et al.* (2013) in terms of an extended cooling period and slower rewarming did not improve outcome. In the study by Hutchinson *et al.* (2008), there was higher incidence of hypotension and low CPP during rewarming in the hypothermia group, and higher risk of unfavorable outcome in a subgroup of patients over 7 years of age, with a mortality rate of 21% in the hypothermia group and 12% in the normothermia group ($p = 0.06$). In a *post hoc* analysis, Hutchison *et al.* (2010) suggested that hypotension and low CPP may explain the unfavorable outcome with hypothermia.

A recent review summarized that there is no support today for the use of hypothermia in the treatment of children with TBI (Bhalla *et al.*, 2012). This conclusion on therapeutic hypothermia agrees with that from a Cochrane analysis from 2009 for both adults and children (Sydenham *et al.*, 2009). They found 23 trials with acceptable entry criteria, but only 8 fulfilled the required level of quality, and in these 8 studies the patients treated with hypothermia were slightly more prone to die.

GCS at Admission

Some studies in this review found that severity of brain injury (GCS score) at admission influenced the therapeutic effect of hypothermia, while others did not. Subgroup analysis in four studies found that hypothermia had no benefit in patients with GCS 3–4 (Gal *et al.*, 2002; Polderman *et al.*, 2002; Inmasu *et al.*, 2006; Yan *et al.*, 2010). It may be that patients with GCS 3–4 are so severely injured that they are unable to benefit from hypothermia. If so, trials including a study population with a low mean GCS are more unlikely to show beneficial effects of hypothermia. However, Liu *et al.* (2006) and Qiu *et al.* (2007) both with a high percentage ($> 50\%$) of patients with GCS 3–5 found beneficial effects of hypothermia. Neither Clifton *et al.* (2011) nor Hutchison *et al.* (2008) found an interaction between GCS at admission and outcome by hypothermia.

Intracranial Lesion and Neurosurgery

A subgroup analysis from the study by Clifton *et al.* (2011) showed that patients who underwent surgical removal of intracranial hematomas showed beneficial effects by hypothermia. This hypothesis was supported by other studies included in this review (Gal *et al.*, 2002; Polderman *et al.*, 2002; Inamasu *et al.*, 2006; Liu *et al.*; 2006; Qiu *et al.*, 2007; Lee *et al.*, 2010). Neurosurgery and type of brain injury are closely linked as hematomas are surgically removed, whereas patients with diffuse brain injury are exposed to surgery to a less extent.

Intracranial Pressure

All 14 studies on adults, except the one by Clifton *et al.* (2011), found lower ICP values in the hypothermia group than in the control group. Clifton *et al.* (2011) showed that episodes of raised ICP were significantly more frequent in the hypothermia group than in the normothermia group. A goal-directed therapy on ICP by hypothermia was used in two adult studies, both indicating positive effects (Polderman *et al.*, 2002; Zhi *et al.*, 2003). In these studies, the management was tailored individually, with cooling up to ICP had normalized. The negative study by Clifton *et al.* (2011) and the positive study by Zhi *et al.* (2003) used equal rewarming rates, but had conflicting results regarding ICP levels and outcome. Note that no beneficial effect on outcome was observed with similar reduction in ICP following reduced metabolic rate by barbiturate treatment (Roberts and Sydenham, 2012).

Four of the pediatric studies reported ICP (Biswas *et al.*, 2002; Adelson *et al.*, 2005; Hutchison *et al.*, 2008; Li *et al.*, 2012). Li *et al.* (2012) reported that ICP was lower in the hypothermia group at all time points tested, while Biswas *et al.* (2002) noted just a trend of lower ICP levels in the hypothermia group. Hutchison *et al.* (2008) reported a significantly lower ICP during the cooling period and a significantly higher ICP during rewarming in the hypothermia group. Adelson *et al.* (2005) showed similar results, but ICP differed between the groups only within the first 24 hours.

It is difficult to draw any general conclusion from the studies analyzed in this review regarding correlation between ICP, rewarming rate, rebound increase in ICP, and outcome. The newly started Eurotherm3235 hypothermia trial specifically evaluating the effect of ICP on outcome (Andrews *et al.*, 2013) will be a welcome contribution to bring light on this issue.

Complications

Ten of the 14 studies in adults had data on complications, which can be referred to hypothermia. The type of complications included coagulopathy, cardiovascular complications, and pneumonia (Liu *et al.*, 2006; Qiu *et al.*, 2006, 2007). Qui *et al.* (2006, 2007) and Liu *et al.* (2006) reported an increase in thrombocytopenia in hypothermic patients. In addition, Qui *et al.* (2006, 2007) reported an increase in pulmonary infections with hypothermia. A Cochrane analysis also concluded that hypothermia can be associated with complications, especially pulmonary complications (Sydenham *et al.*, 2009).

No difference in complications between hypothermia and normothermia was reported in four of the five pediatric studies (Biswas *et al.*, 2002; Adelson *et al.*, 2005, 2013; Hutchison *et al.*, 2008). One of the pediatric studies (Adelson *et al.*, 2005) found a trend of increased arrhythmias in the hypothermia group.

Limitations

Like most clinical studies, the hypothermia studies analyzed in this review had limitations and the generalizability of the data is limited. Several authors did not report if the difference in outcome between groups was significant or not, and the numbers of patients were small in several studies.

The management protocols differed with different inclusion criteria, patient characteristics, and cooling and rewarming performance, and the risk of confounders was high. Penetrating trauma, multiple injuries, hypotension, and acute

TABLE 2. RESULTS OF INCLUDED TRIALS: MORTALITY AND NEUROLOGICAL OUTCOME

	Mortality		*Neurological outcome*	
Study	*Hypo vs. normo (%)*	p-*value*	*Hypo vs. normo (%)*	p-*value*
Suehiro *et al.* (2014)	34.0 vs. 30.7	NS	44.7 vs. 25.3[a]	0.01
Zhao *et al.* (2011)	2.5 vs. 9.8	NS	75 vs. 51.2[a]	0.04
Clifton *et al.* (2011)	23 vs. 18	0.52	60 vs. 56[b]	0.67
Yan *et al.* (2010)	31.5 vs. 38.7	NR	41.1 vs. 37.3[a]	NR
Lee *et al.* (2010)	6.7, 7.1 vs. 12.5	0.818	60, 71 vs. 50[a]	0.04
Harris *et al.* (2009)	50 vs. 30.8	0.43	NR	NS
Qui *et al.* (2007)	22.5 vs. 32.5	NR	70 vs. 47.5[a]	0.04
Liu *et al.* (2006)	27.3, 28.6 vs. 52.2	<0.05	72.7, 57.1 vs. 34.8[a]	<0.05
Qui *et al.* (2006)	20.0 vs. 28.9	0.327	68.9 vs. 46.7[a]	0.03
Inamasu *et al.* (2006)	33.3 vs. 6.7	<0.05	27.8 vs. 6.7[a]	<0.05
Zhi *et al.* (2003)	25.7 vs. 36.4	<0.05	38.8 vs. 19.7[a]	<0.05
Gal *et al.* (2002)	13 vs. 33	NR	87 vs. 47[a]	NR
Polderman *et al.* (2002)	62.5 vs. 72.2	<0.05	15.6 vs. 9.7[a]	<0.02
Clifton *et al.* (2001)	28 vs. 27	0.79	57 vs. 57[b]	1.0
Adelson *et al.* (2013)[c]	15 vs. 5	0.15	42 vs. 42[b]	NR
Li *et al.* (2009)[c]	8.3 vs. 20	0.5714	NR	NR
Hutchison *et al.* (2008)[c]	21 vs. 12	0.06	31 vs. 22[b]	0.14
Adelson *et al.* (2005)[c]	13.5 vs. 18.4	NR	NR	0.54
Biswas *et al.* (2002)[c]	30 vs. 0	NR	NR	>0.1

[a] Neurologic outcome presented as difference in favorable/good neurologic outcome (Glasgow Outcome Scale score 4–5) between groups.

[b] Neurologic outcome presented as difference in unfavorable/poor neurologic outcome (Glasgow Outcome Scale score 1–3/Pediatric Cerebral Performance Category scale 4–6) between groups.

[c] Pediatric trial.

Normo, normothermia; NS, not significant.

isolated epidural hematomas are examples of inclusion criteria used in some studies but not in others. The follow-up time after the accident varied between the studies.

Several of the studies reviewed could not be assessed as high quality because of relatively few patients included, unclear randomization, unclear allocation concealment, and/or insufficient blinding of outcome assessment.

Summary

The studies included showed conflicting results regarding mortality and neurological outcome and varied in quality. Several trials showed improved neurological outcome with hypothermia and a trend of lower mortality rates, but the best-performed studies showed no difference in outcome or even a tendency of worse outcome, especially in the pediatric population. Adverse effects of hypothermia in TBI patients, such as pneumonia, coagulation disturbances, rebound increase in ICP, and stress-induced decrease in oxygenation of hypoxic areas, may counteract its neuroprotective effects. We conclude that we still lack scientific support for the use of therapeutic hypothermia as a first-tier therapy in TBI patients for both adults and children, but it may still be an option as a second-tier therapy for refractory intracranial hypertension.

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