



# Therapeutic hypothermia in stroke and traumatic brain injury

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Therapeutic hypothermia (TH) is considered to improve survival with favorable neurological outcome in the case of global cerebral ischemia after cardiac arrest and perinatal asphyxia. The efficacy of hypothermia in acute ischemic stroke (AIS) and traumatic brain injury (TBI), however, is not well studied. Induction of TH typically requires a multimodal approach, including the use of both pharmacological agents and physical techniques. To date, clinical outcomes for patients with either AIS or TBI who received TH have yielded conflicting results; thus, no adequate therapeutic consensus has been reached. Nevertheless, it seems that by determining optimal TH parameters and also appropriate applications, cooling therapy still has the potential to become a valuable neuroprotective intervention. Among the various methods for hypothermia induction, intravascular cooling (IVC) may have the most promise in the awake patient in terms of clinical outcomes. Currently, the IVC method has the capability of more rapid target temperature attainment and more precise control of temperature. However, this technique requires expertise in endovascular surgery that can preclude its application in the field and/or in most emergency settings. It is very likely that combining neuroprotective strategies will yield better outcomes than utilizing a single approach.

**Keywords:** hypothermia, stroke, traumatic brain injury, neuroprotection

## INTRODUCTION

The use of therapeutic hypothermia (TH) as a treatment option for acute neurological injury has evolved over the past century (Krieger et al., 2001). In the 1930s, successful resuscitation following prolonged cold water asphyxia in drowning victims was reported (Gunn and Thoresen, 2006; Linares and Mayer, 2009), which raised the possibility that hypothermia provided a neuroprotective effect in the case of anoxic brain injury (Linares and Mayer, 2009). The first report of TH as a treatment for patients with traumatic brain injury (TBI) was published in 1943 (Fay, 1943), and that was followed by reports from several other investigators touting its potential neuroprotective effects in acute neurological injuries (Metz et al., 1996; Krieger et al., 2001; Schwab et al., 2001; Polderman, 2004; Kollmar et al., 2009). In 1952 at the University of Minnesota, Dr. John Lewis closed an atrial septal defect in a 5-year-old girl using total-body hypothermia. The child's body was cooled to 28°C with a cooling blanket and rewarmed in a tank of warm water (Gott, 2005). Currently, clinical application of TH is utilized in during open-heart surgery and after global cerebral ischemia associated with cardiac arrest and prenatal asphyxia (Lazaro and Prabhakaran, 2008; van der Worp et al., 2010). Although TH is instituted after other acute neurological injuries such as stroke and TBI, the efficacy of its routine use for these conditions remains unproven (Miyazawa et al., 2003). Additionally, complications including a high risk of infection, cardiac arrhythmias,

thrombocytopenia, hypotension, hypokalemia, pancreatitis, gastrointestinal ulcer, liver dysfunction, coagulopathy, and acute heart failure have been reported (De Georgia et al., 2004; Alty and Ford, 2008; Varon and Acosta, 2008; Yenari et al., 2008; Den Hertog et al., 2009). The focus of this review will be to discuss the pathophysiological rationale and evidence-based literature supporting the use of TH in treatment of patients with acute ischemic stroke (AIS) and TBI.

## PATHOPHYSIOLOGY OF HYPOTHERMIA

Hypothermia exerts complex effects on human physiology. In conscious, non-intubated patients it can be difficult to induce TH without pharmacological interventions because the human body mounts vigorous thermoregulatory defenses. These thermoregulatory mechanisms substantially increase metabolic activity within the body, which may be harmful or at least counterproductive as they impede the induction of TH (Busto et al., 1989a; Bandschapp and Iazzo, 2011).

Thermoregulatory mechanisms can be divided into behavioral and hypothalamic controlled autonomic responses. The behavioral components of these responses (e.g., protection by clothes, shelter, shade, or air conditioning) are ultimately under our conscious control. In clinical settings these behavioral controls are often usurped by healthcare providers (Busto et al., 1989a; Bandschapp and Iazzo, 2011). The effects or responses governed by the

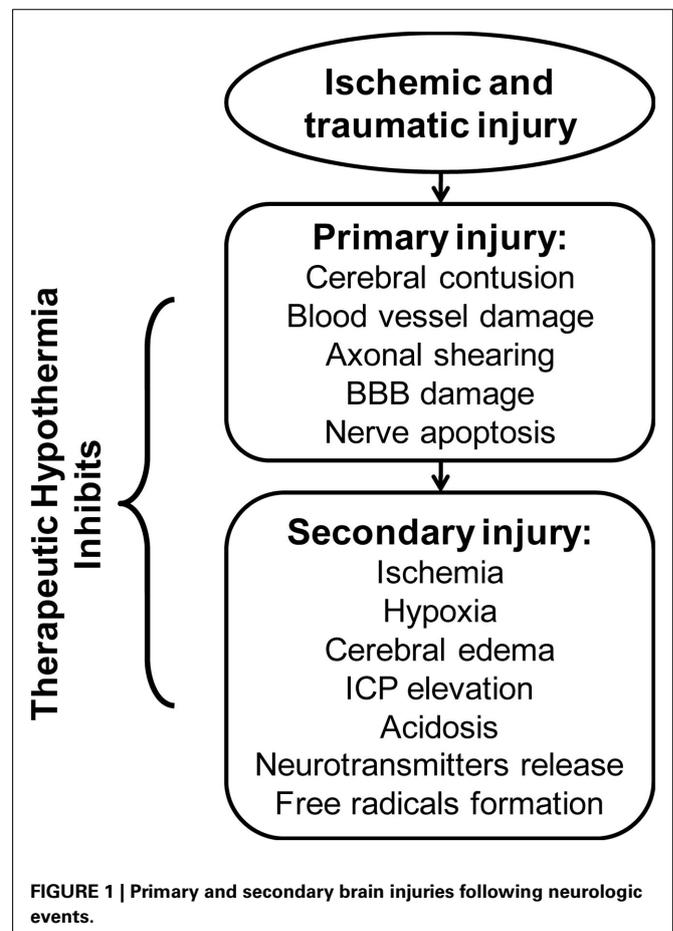
autonomic nervous system are the primarily activated responses to cold include arteriovenous shunting or induced vasoconstriction and shivering. In general, cutaneous vasoconstriction is initiated once core temperature decreases to about 36.5°C, and significant shivering starts at around 35.5°C. It should be noted that while most blood vessels constrict in response to regional hypothermia, arteriovenous shunting is relatively resistant to local temperature changes and seems to be mainly controlled by central mechanisms (Sessler, 2008). In infants, non-shivering thermogenesis of “brown fat” follows as the next elicited effector response. Interestingly, however, thermogenesis via shivering is totally absent in the newborn and not fully effective until several years of age (Brooke et al., 1973). In contrast, non-shivering thermogenesis is considered to have a relatively minor or marginal physiological role in adults (Jessen, 1980). By definition, shivering is involuntary, oscillatory muscle activity that greatly increases metabolic heat production to counteract hypothermia (Iampietro et al., 1960). Notably, in a hypothermic patient, the elicitation of forceful shivering can increase metabolic heat production several-fold, which exacerbates the patient’s condition. Therefore, one needs to consider modulating this response either with muscle paralysis and/or lowering the shivering threshold (Busto et al., 1989a; Bandschapp and Iaizzo, 2011). Muscle paralysis is the most effective way to stop shivering, but increases risk of many adverse events (AEs) including inability to detect changes in the neurological exam, high risk of pneumonia, and prolonged ventilation. Thus, using a pharmacological approach to lower the shivering threshold in awake patients may considerably reduce the need for heavy sedation, paralytics and, therefore, the need for ventilatory support (Guluma et al., 2006). Some pharmacological agents that are used to inhibit shivering include buspirone, meperidine, clonidine, magnesium, and dexmedetomidine (Xue and Huang, 1992; Karibe et al., 1994; Bandschapp and Iaizzo, 2011; Kallmünzer et al., 2011). Several reported pharmacological anti-shivering protocols have allowed investigators to achieve the target temperature (TT) without using heavy sedation or paralytics, often obviating the need for mechanical ventilation (Xue and Huang, 1992; Karibe et al., 1994; Bandschapp and Iaizzo, 2011; Kallmünzer et al., 2011). In some studies, buspirone and meperidine in combination synergistically decreased the shivering threshold to 33°C, with, notably, minimal sedation or respiratory depression (van Breda et al., 2002; Bandschapp and Iaizzo, 2011). Based on these findings, Lyden et al. (2005) suggested that prophylactic administration of oral buspirone plus intravenous (IV) meperidine could effectively prevent shivering to achieve the TT in awake patients. Another useful technique to reduce shivering is surface counter warming using heating blankets (Guluma et al., 2008). Bandschapp and Iaizzo (2011) combined surface counter warming of the hands and/or face with the use of anti-shivering drugs.

Classically, the primary neuroprotective benefit of TH has been attributed to a reduction in the cerebral metabolic rate of oxygen (CMRO<sub>2</sub>), which is related to neuronal glucose and oxygen consumption and lactate production. In other words, TH may reduce energy depletion by lowering the CMRO<sub>2</sub> and improving glucose utilization (Yenari et al., 2008; Liu and Yenari, 2007). Reportedly, brain oxygen consumption decreases by 5% per 1°C decrease in body temperature. Additionally, slowed metabolism following TH

reduces interstitial lactate accumulation and maintains physiological tissue PH balance. It has been shown that for every 1°C decrease in temperature, the pH increases by 0.016 (Varon and Acosta, 2008). This lends support to the notion that TH may reduce cerebral injury by reducing acidosis. However, in another study, no decrease was detected in cerebral lactate level following TH (Busto et al., 1989a). Therefore, one can conclude that TH produces neuroprotective effects through other mechanisms (Busto et al., 1989a).

Beyond reduction of CMRO<sub>2</sub>, the other neuroprotective mechanisms of TH include: (1) preservation of high-energy organic phosphates; (2) slowed accumulation of lactic acid and other neurotoxins; (3) enhanced glucose utilization; (4) modulation of gene expression; (5) facilitation of anti-inflammatory responses and anti-apoptotic pathways; (6) reduction of intracranial pressure (ICP); (7) stabilization of the blood–brain barrier; (8) inhibition of free radical productions; and (9) reduction of excitotoxic neurotransmitters such as glutamate (Jiang et al., 1992; Miyazawa et al., 2003; Olsen et al., 2003; van der Worp et al., 2007; Varon and Acosta, 2008; Yenari et al., 2008).

In patients presenting with cerebral ischemia, TH may minimize the extent of injury (Figure 1) by modulating several steps of the ischemic cascade (Lazzaro and Prabhakaran, 2008; Linares and Mayer, 2009). More specifically, in an experimental study using positron emission tomography scan to evaluate the effect



**FIGURE 1 | Primary and secondary brain injuries following neurologic events.**

of TH after AIS, reduction in CMRO<sub>2</sub> was coupled with decreases in cerebral blood flow (CBF) and minimization of brain tissue necrosis volume (Sakoh and Gjedde, 2003). Furthermore, TH may reduce neuronal excitotoxicity following ischemic depolarization by blocking glutamate and dopamine release (Nakashima and Todd, 1996). For example, in an experimental study, Busto et al. (1989b) demonstrated that mild hypothermia, with a TT between 35 and 36°C, significantly reduced cerebral dopamine and glutamate release, thus attenuating neurotoxicity. In addition, decreased glutamate accumulation leads to reduced calcium influxes and lipid peroxidation, which then attenuates free radical production (Nakashima and Todd, 1996). Furthermore, TH may inhibit free radical activity following cerebral ischemia by enhancing levels of endogenous antioxidants (Maier et al., 2002). Hashimoto et al. (2004) evaluated the effect of TH on free radical production in a rodent model of cerebral ischemia by cerebellar microdialysis measurements. The experiment revealed temperature-related reduction of free radical production associated with attenuated neuronal damage in both the ischemic and reperfusion phases (Maier et al., 2002; Hashimoto et al., 2004). Finally, TH may favor up-regulation of stress responsive genes, which produce anti-apoptotic proteins such as β-catenin, which translocate into the nuclei and regulate gene expression, favoring cell survival (Akaji et al., 2003; Lazzaro and Prabhakaran, 2008; Zhang et al., 2008).

It is suggested that CBF is reduced through arteriolar vasoconstriction during TH, resulting in decreased ICP (Bernard and Buist, 2003; Varon and Acosta, 2008; Yenari et al., 2008). However, in a clinical study of patients with severe TBI, inducing moderate TH (32–33°C) resulted in decreased ICP, though CBF was not changed significantly during the therapy; this suggests restoration of blood brain barrier (BBB) function and subsequent reduction in cerebral edema as an underlying mechanism for drop in ICP (Metz et al., 1996). More specifically, pericyte migration from the microvasculature following reperfusion injury normally results in disruption of BBB (Liu and Yenari, 2007; Lazzaro and Prabhakaran, 2008). In the rodent model, however, the induction of TH in ischemic brain injury inhibited the separation of pericytes from basement membrane, thereby preserving BBB integrity (Duz et al., 2007). Therefore, the intact BBB prevents the leakage of plasma proteins into the brain interstitium post-ischemia possibly reducing cerebral edema formation and the associated rise in ICP. In summary, TH mounts a multi-faceted cascade of neuroprotective mechanisms after cerebral ischemia and TBI (see **Figure 1**).

### THERAPEUTIC HYPOTHERMIA INDUCTION

The optimal induction method of TH is currently unknown. Desirable characteristics of the TH method include safety, rapid cooling speed, easy implementation, widespread availability, and low financial costs. It is almost certain that a multimodal approach will be required, likely combining pharmacological agents and physical techniques, and keeping in mind the transition from the prehospital to hospital setting (Den Hertog et al., 2009).

### PHARMACOLOGICAL COOLING

Pharmacological agents include antipyretics and non-steroidal anti-inflammatory agents. Unfortunately, the use of non-steroidal

anti-inflammatory drugs (i.e., ibuprofen) or antipyretic drugs (i.e., acetaminophen) for TH has shown only a modest reduction in temperature (Dippel et al., 2001, 2003; Koennecke and Leistner, 2001; Kasner et al., 2002; Aiyagari and Diringier, 2007; Linares and Mayer, 2009), and therefore is insufficient alone to produce clinically significant hypothermia.

### MECHANICAL COOLING

There are many options available for systemic or regional body cooling. Systemic methods include either surface cooling or intravascular cooling (IVC). Surface cooling techniques such as water-circulating cooling blankets, ice-packs, water mattresses, ice-water and alcohol baths, whole body ice rubs, electric cooling fans, and/or forced air cooling have been studied in numerous small clinical trials (Schwab et al., 1998, 2001; Kammersgaard et al., 2000; Krieger et al., 2001; Abou-Chebl et al., 2004; Mayer et al., 2004; Jordan and Carhuapoma, 2007; Den Hertog et al., 2009). Endovascular cooling includes intravenous ice-saline infusion into peripheral or central veins, and active cooling catheters intra-arterially or intravenously (Lenhardt et al., 2009).

### SURFACE COOLING

Surface cooling is easy to implement, but usually induces severe shivering which may require heavy sedation and/or paralysis with neuromuscular blockade (Lazzaro and Prabhakaran, 2008). In addition, it is often challenging to maintain body temperature at a desired level via surface cooling. In one study, surface cooling induced hypothermia led to overcooling in 9 of 10 subjects (Zweifler et al., 2003; Guluma et al., 2006). However, active surface cooling using the Arctic Sun Temperature Management System (Medivance, Louisville, CO, USA) was more effective than conventional surface cooling methods, such as the cooling-blanket, for controlling fever in critically ill neurologic patients (Mayer et al., 2004). This device has a feedback mechanism to actively regulate the body temperature to a specific target. The main limitation of this device is that it is somewhat labor intensive, and the disposable cooling pads are expensive.

Based on the limitation of general surface cooling, interest has focused on regional cooling, such as by using selective head and/or neck cooling (Wang et al., 2004; Qiu et al., 2006). In one study, head cooling lowered temperature to 34°C, but took several hours to reach, likely related to low skull thermal conductivity (Harms et al., 2008). Additionally, while selective head cooling may reduce the superficial cortical temperature, it may not cool deeper brain structures to the same level (Chen et al., 2009). However, concurrent neck cooling was found to increase cooling efficiency of lowering core body temperature (Keller et al., 2009). A novel method of prehospital trans-nasal evaporative cooling has been applied in patients with witnessed cardiac arrest recently. In this method, a liquid coolant–oxygen mixture is sprayed into the nasal cavity, which rapidly evaporated with high-flow oxygen, results in significant cooling of the nasal passages and brain. This trial presented the feasibility of this method with improvement in the time intervals required to cool patients. However, some device-related AEs including nasal whitening, epistaxis, and peri-orbital emphysema have been occurred (Castren et al., 2010).

## INTRAVASCULAR COOLING

Intravascular cooling has some advantages to surface cooling, but also carries certain risks as it is usually an invasive technique. In general, as no surface equipment such as cooling blanket or pads are needed, one can institute surface counter warming, resulting in the attenuation of the shivering response while concurrently allowing for efficient cooling of the core blood volume (Polderman et al., 2005; Lazzaro and Prabhakaran, 2008). The average time to achieve the TT has been shown to be considerably shorter (~70 min) using IVC compared to surface cooling (3–8 h; Keller et al., 2003). A possible explanation for this is that surface cooling triggers cutaneous vasoconstriction which reduces conduction surface area (Guluma et al., 2006). In contrast, a local intra-arterial infusion of cold saline may achieve TT within a few minutes. The rapid attainment of the TT may enhance neuroprotection and also expand the therapeutic time-window for other treatment strategies, but further data is needed to confirm this (Konstas et al., 2007). However, the required experience with endovascular techniques prevents an easy widespread application (van der Worp et al., 2010). Some possible specific adverse effects of IVC include a higher risk for infection, deep venous thrombosis (DVT), and vascular dissection (Schwab et al., 2001). Simosa et al. (2007) evaluated the risks of DVT with duplex sonogram in TBI patients who underwent intravascular TH. They observed a DVT rate of 33% if the catheter were removed within 4 days but the rate was increased up to 75% when the catheter was removed after 4 days. Therefore, it may be prudent to monitor patients closely with duplex ultrasonography for DVT if an IVC method is used. Some novel techniques of invasive cooling induction are currently under investigation. A few experimental studies have evaluated the technical feasibility of epidural surface cooling induction. The outcomes were promising in attaining the rapid TT with unchanged physiologic and hemodynamic variables (Zweifler et al., 2003; Qiu et al., 2006).

## CORE BODY TEMPERATURE ASSESSMENT

The best method for assessing core body temperature is uncertain. Currently, core body temperature is estimated using a variety of probes, including rectal, tympanic, bladder, esophageal, or vaginal probes (Nolan et al., 2003). Unfortunately, the temperatures recorded in these different sites may vary by up to several degrees, and it is not clear how they correlate with brain or core body temperature. For example, in one study it was observed that rectal or bladder temperatures were 1–2°C lower than monitored brain temperatures, and at temperatures above 38 or below 36°C, the differences became even greater (Henker et al., 1998). Thus, further investigations are needed to determine

clinically applicable, non-invasive, accurate ways to approximate brain temperature.

## THERAPEUTIC HYPOTHERMIA IN STROKE

The use of TH has been well established to improve survival with favorable neurological outcome in the case of global cerebral ischemia after cardiac arrest or perinatal hypoxia-ischemic insult; however, the efficacy of TH for treating focal cerebral ischemia has not yet been well studied (Abate et al., 2008). However, in reported animal studies, TH has consistently reduced infarct sizes when applied before or early after the onset of cerebral ischemia (Xue and Huang, 1992; Karibe et al., 1994).

In the last decade, various clinical trials have attempted to evaluate the potential benefits of utilizing pharmacological and/or physical TH in AIS (Tables 1 and 2). More specifically, in such pharmacological trials, the efficacies of low- and high-dose administration of paracetamol, metamizole, or ibuprofen have been assessed (Dippel et al., 2001, 2003; Koennecke and Leistner, 2001; Kasner et al., 2002; van Breda et al., 2002; Kallmünzer et al., 2011). A pooled analysis showed only a modest reduction of 0.2°C temperature 24 h after administration. Therefore, as expected, clinical trials did not show any significant clinical benefit with these agents (Den Hertog et al., 2009).

Given the lack of efficacy of the aforementioned pharmacological cooling protocols, we now turn our attention to physical cooling trials. In one such report, Schwab et al. (1998) applied surface cooling for TH in 25 patients with malignant middle cerebral artery infarction and observed beneficial reduction of ICP. Furthermore, the treated patients showed more favorable outcomes and reduced mortality rates than historical controls with similar stroke severity. Notably, nearly half of the deaths in TH-treated patients occurred during the rewarming phase, possibly in relation to a rebound in ICP. It was suggested that a longer rewarming period may be needed to diminish the rebound ICP elevation (Schwab et al., 2001).

Other clinical trials have evaluated the optimal duration of TH once the TT is achieved. In the Copenhagen stroke study, investigators assessed the efficacy of 6 h of surface cooling in 17 AIS patients (Kammersgaard et al., 2000). Unfortunately, no benefit in terms of outcome was observed. It has been suggested, however, that a longer hypothermia duration of 48–72 h may be required to reduce the formation of cerebral edema which occurs the most during the first 72-h after symptom onset (Georgiadis et al., 2001). Concerns, however, include the correlation between increased duration of TH and increased number of AEs; therefore, limiting TH to 24 h may be better (Kammersgaard et al., 2000).

**Table 1 | Published studies on the role of pharmacological TH in stroke patients.**

Investigator	Year	No of cases	Intervention	Mean °C reduction
Kallmünzer et al.	2011	77	Paracetamol, Metamizole, calf packing	NA
Dippel et al.	2003	75	6000 mg Paracetamol/day, 2400 mg Ibuprofen/day	0.3°C
Kasner et al.	2002	39	3900 mg Paracetamol/day	0.22°C
Dippel et al.	2001	75	6000 mg Paracetamol/day, 3000 mg Paracetamol/day	0.4°C
Koennecke and Leistner	2001	42	4000 mg Acetaminophen/day	NA

**Table 2 | Published studies on the role of surface and intravascular TH in stroke patients.**

Study	Year	No of cases	Intervention	Target (°C)	Time to target (°C)	Rewarming time	Side effect	Outcomes
Hemmen et al.	2010	28	Intravascular hypothermia + fibrinolysis	33	67 min	0.3°C/h	Pneumonia in cases	No difference
Kollmar et al.	2009	10	Iced cold saline infusion	35.4	52 min	NA	Well tolerated	NIHSS improved (4 scores)
Guluma et al.	2008	18	Intravascular cooling	33	–	12 h	Higher NIHSS in the case group	Reduction of edema
Guluma et al.	2006	10	Intravascular cooling	33.4	1.7 h	0.3°C/h	NA	No shivering
Lyden et al.	2005	16	Intravascular cooling + fibrinolysis	33	7 h	12 h	DVT	NA
De Georgia et al.	2004	18	Intravascular cooling	35	77 min	NA	NA	Decreased mean diffusion-weighted imaging lesion growth in cases
Schwab et al.	2001	50	Surface cooling	33	6.5 h	17 h	Pneumonia, secondary rise of ICP	Relatively decreased mortality
Georgiadis et al.	2001	6	Intravascular cooling	32.2–33.4	3 h	NA	Bradycardia infection	NA
Krieger et al.	2001	10	Cooling blanket + fibrinolysis	32	3.5 h	0.21°C/h	Sinus bradycardia	NA
Kammersgaard et al.	2000	17	Surface cooling	35.5	6 h	NA	Pneumonia	Insignificant lower mortality rate and improved clinical outcomes in cases
Schwab et al.	1998	25	Surface cooling	33	3.5–6.2 h	18 h	Pneumonia	Reduction of ICP

Georgiadis et al. (2001) evaluated the feasibility of IVC in six patients with AIS. The clinical outcomes were considered equal to those obtained by surface cooling, demonstrating IVC as a viable option for TH (De Georgia et al., 2004; Lyden et al., 2005; Guluma et al., 2006). Moreover, it should be mentioned again that IVC allows for concurrent use of surface warming to reduce shivering (Guluma et al., 2006). For example, in a pilot study by Kollmar et al. (2009), rapid infusion of ice-cold saline combined with anti-shivering pharmacological therapy in 10 AIS patients significantly improved discharge NIH stroke scale scores without increasing major side effects. Similarly, Lyden et al. (2005) evaluated several anti-shivering methods in 10 awake patients who underwent IVC after AIS. They reported that a combination of oral buspirone with IV meperidine (load and maintenance) in addition to surface warming blankets allowed for the efficient induction of TH while minimizing shivering.

Recently, the COOL AID study evaluated the feasibility of IVC in 18 AIS patients compared to 22 control AIS patients (De Georgia et al., 2004). It was reported that there was less diffusion-weighted imaging volume growth in the hypothermic patients compared to the control group, but the long-term clinical outcomes were not significantly different. Nevertheless, this pilot study was not powered for efficacy, and therefore a larger-scale trial may be warranted. In another clinical study, Guluma et al. (2008) evaluated the role of TH using IVC in 18 AIS patients. They found that patients who were effectively cooled to a temperature of less than

34.5°C within 8 h of cooling initiation had a decreased amount of cerebral edema compared to control patients or those who did not achieve the TT. In contrast, Hemmen et al. (2010) studied the feasibility and safety of TH combined with IV t-PA after AIS among patients who were randomized to t-PA and TH ( $n = 28$ ), or t-PA ( $n = 30$ ) alone. They reported that there were no significant differences in symptomatic ICH rates, modified Rankin Scale scores, or mortality at 3 months; however, more patients in the TH group developed pneumonia ( $p = 0.001$ ). The relative lack of efficacy in the TH group may be related to relatively long induction times (median 7 h) required to achieve the TT and the small sample size in the study.

It looks as though TH could be an appropriate adjuvant therapy to t-PA for AIS. It also has a potential for utilization in combinational therapeutic strategies with other neuroprotective medication such as caffeine or hemicraniotomy in malignant supratentorial infraction (Els et al., 2006; Martin-Schild et al., 2009). However, based on the relatively small clinical trials available in the literature, it is apparent that much work is needed to clarify many issues for AIS patients. These include the optimal depths and durations of cooling, improved techniques to reach TT in an optimized time-window, clinically safe rewarming rates, and/or the best anti-shivering measures as discussed previously (MacLellan et al., 2009). Only once the practical aspects of TH in AIS patients are worked out can the efficacy of TH possibly be determined in a large, multicenter clinical trial.

## THERAPEUTIC HYPOTHERMIA IN TBI

From a historical perspective, TH for TBI patients was first introduced by Fay (1943) and Marion et al. (1997). Since then, several case series have reported heterogeneous outcomes for patients with TBI receiving TH (Rosomoff and Holaday, 1954; Lazorthes and Campan, 1958; Hendrick, 1959; Sedzimir, 1959; Drake and Jory, 1962; McIntyre et al., 2003). Nevertheless, despite numerous successes of TH in animal models, the efficacy of routine TH for TBI patients in the clinical setting is not definitely established (Buchan and Pulsinelli, 1990; Minamisawa et al., 1990; Clifton et al., 1991; Dietrich et al., 1994). In 1993, three different TBI trials demonstrated the feasibility and efficacy of TH to improve clinical outcomes in small trials (Clifton et al., 1993; Marion et al., 1993; Shiozaki et al., 1993). In 1997, a clinical trial evaluated the impact of surface cooling on 40 TBI patients (Marion et al., 1997). Although there was no efficacy for the cohort of patients with the most severe TBI [i.e., Glasgow Coma Scale (GCS) of 3–4 on admission], TH was found to benefit patients with initial GCS of 5–7 in terms of their long-term clinical outcome and mortality. This clinical trial showed that the interleukin-1 $\beta$  and glutamate levels in CSF were significantly reduced in the hypothermic group even after rewarming. Interestingly, the glutamate levels in the patients who did not benefit from hypothermia (GCS of 3 or 4) were similar to those with corresponding GCS scores in the normothermic group. Subsequently, in a larger study performed by Clifton et al. (2001;  $n = 392$ ), fewer patients in the hypothermia group had elevated ICP. They did, however, have more complications and longer hospital stays, especially in patients older than 45-years. Similarly, Marion et al. (1997) found no improvement in neurological outcomes or survival in TH patients with initial GCS of 5–8. It should perhaps be considered that initial differences in the baseline characteristics of the patients in these separate studies might be a primary underlying factor influencing the differing results. For example, in the study by Marion et al. (1997) a high proportion of patients in normothermic group were described as being in a hypothermic state at the time of admission and were thus actively warmed after admission, which itself may have led to a poorer outcome (Clifton et al., 2001).

In an effort to clarify the heterogeneous and conflicting results regarding the efficacy of TH for patients with TBI, a systematic review was performed in 2003 which pooled data from 12 published clinical trials. Overall, this analyses included 1069 patients who were split into a hypothermia group ( $n = 543$ ) and a control group ( $n = 526$ ; McIntyre et al., 2003). From this retrospective analysis, it was suggested that inducing TH for 24 h significantly reduces the risk of poor neurological outcome. Furthermore, patients who received TH for more than 48 h had increased survival. In addition, this analysis suggested that greatest clinical benefits were derived when patients were cooled to a TT of 32–33°C. Subsequent to this report, Tokutomi et al. (2009) evaluated the clinical outcomes and systemic complications of TH in two different groups of patients with TBI who were cooled to either 35 or 33°C. Despite the findings from the previous systematic review (McIntyre et al., 2003), Tokutomi and co-workers' study paradoxically showed lower systemic complication and mortality rate in the milder hypothermia (35°C) group. These outcomes were similar to those observed by Shiozaki et al. (2003) who did

not find any benefit in cooling TBI patients from 34 to 31°C with refractory ICP, defined as being higher than 40 mmHg despite first line treatments.

It should be considered that severe TBI patients may have physical restrictions imposed on their clinical management by systemic trauma, potentially making surface cooling difficult to implement in such individuals (Sahuquillo et al., 2009). With this scenario in mind, Harms et al. (2008) applied a cooling helmet in TBI patients. This approach was considered to have failed, however, as it was not effective in reaching the target brain temperature in most patients. **Table 3** summarizes other approaches of using TH in TBI patients. In the IntraCool study in which therapy was applied to IVC patients with severe TBI and refractory elevated ICP ( $n = 28$ ), a significant reduction in ICP and mortality rate was observed (Sahuquillo et al., 2009). Likewise, a study by Puccio et al. (2009) showed that even an induced normothermia protocol utilizing IVC ameliorated secondary brain injuries, perhaps by reducing the ICP. In 2010, a comprehensive review evaluating 23 clinical trials including results from 1614 randomized patients reported that the TH group had better neurological outcomes and reduced mortality rate (Sydenham et al., 2009). Significant benefit was only found in trials with open label or uncertain masking designs, however, which, notably, may have led to examiner bias. Importantly, in the nine of these trials with adequate masking procedures, no significant benefit in clinical outcomes was observed. Similarly, a meta-analysis of six clinical trials of TBI patients revealed that treated individuals with hypothermia had a 46% increased likelihood of favorable neurological outcome, defined as a Glasgow Outcome Score of 4–5 (Bratton et al., 2007). Despite this increased likelihood of favorable neurological outcome, no significant reductions in all-cause mortality were observed in TH patients. As such, the aforementioned results are in contrast to the 2003 systematic review (McIntyre et al., 2003) that suggested reduced mortality when cooling was maintained for more than 48 h. In response to such reported inconsistencies in the effects of TH on TBI patients, Clifton et al. (2011) recently designed a multicenter, double-blind study to specifically assess the potential neuroprotective effects of early induction of TH on the outcomes of TBI. In this study, the mean time to reach core temperature of 35°C in the patients in the hypothermic group was 2.6 h after injury. Nevertheless, their results did not show any significant superiority in clinical outcomes in the TH group ( $n = 119$ ) when compared to normothermic patients ( $n = 113$ ). Also, inexplicably, a significantly higher proportion of patients in the TH group had episodes of increased ICP. Therefore, there remains a need for further clarification through well-designed clinical trials in such TBI patients to determine which or whether any patient subgroups may benefit from TH.

## DISCUSSION

Currently, protocols to administer TH are well established for patients who suffer out-of-hospital cardiac arrest or for neonates with hypoxic-ischemic encephalopathy (Abate et al., 2008). Clinical outcomes for patient populations with either AIS or TBI that had received TH therapy have yielded conflicting results and therefore no adequate clinical consensus for use in these types of patients has been reached (Abate et al., 2008; Arcure and Harrison,

**Table 3 | Published studies evaluating the role of therapeutic hypothermia in TBI patients.**

Study	Year	No of cases	Cooling method	Target (°C)	Time to Target (°C)	Duration of hypothermia	Rewarming	Outcomes	Side effect
Clifton et al.	2011	52	Surface cooling	33	4.4	48 h	0.5°C/2 h	Improved clinical outcomes in patients with evacuated hematoma	ICP rise
Harms et al.	2008	12	Cooling cap	33	NA	24 h	24 h	Cooling cap was not capable to reach the target temperature	Higher mortality rate in cases
Tokutomi et al.	2009	30 vs. 31	Surface cooling	35 vs. 33	NA	NA	NA	The mortality rate and the incidence of systemic complications tended to be lower in the 35 degree group than 31 degree	–
Sahuquillo et al.	2009	24	Intravascular cooling	32.5	3 h	155.3 h	1°C/day	ICP reduction in refractory cases	Rebound ICP rise arrhythmia
Puccio et al.	2009	21	Intravascular cooling	36.5	NA	72 h	NA	Reduce fever burden	–
Adelson et al.	2005	23	Surface cooling	32–33	4.99 h	48 h	1°C/3–4 h	TH decrease mortality	Arrhythmia rebound ICP rise
Shiozaki et al.	2003	22	Surface cooling	31 vs. 34	3 h	NA	NA	Moderate hypothermia is not effective in improving clinical outcomes in TBI with refractory ICP after mild hypothermia	More sever complication in 31°C
Zhi et al.	2003	198	Surface cooling	32–35	NA	62.4 h	NA	TH reduce mortality and improve prognosis	Less sever complication in TH group
Clifton et al.	2001	199	Surface cooling	33	8 h	48 h	0.5°C/h	Decreased ICP crisis	More hospital stay critical hypotension
Shiozaki et al.	2001	45	Surface cooling	34	NA	48 h	1°C/day	No advantage in TH over normothermia	Pneumonia meningitis

2009). It is noteworthy that recently several systematic reviews, which pooled data from heterogeneous clinical trials with different cooling methods, failed to show any significant improvement in clinical outcomes after induction of hypothermia (Den Hertog et al., 2009; Sydenham et al., 2009). It is important to note, however, that in more recent trials using IVC in awake patients, the reported outcomes are more promising (Guluma et al., 2008; Puccio et al., 2009; Sahuquillo et al., 2009). More specifically, the application of IVC elicited both the capability of more rapid TT attainment and more precise control of temperature (Guluma et al., 2006).

Early intra-ischemia cooling induction is supposed to modify ischemia-induced as well as post-reperfusion cellular abnormalities, but delayed TH induction is thought to target only the post-reperfusion cell death and inflammatory signaling pathways (Lampe and Becker, 2011). In experimental studies, the best chance of neurological recovery has been achieved by inducing hypothermia within 15 min following initiation of ischemia (Kim et al., 2009). This shows that reaching the optimal core body temperature early in the therapeutic window can have a principal impact on the outcome. Typically, the systems to provide IVC are not portable and the therapy can only be initiated after the patient arrives at the hospital. Thus, the imposed delay in treatment may reduce the possibilities for achieving optimal outcome. To overcome this problem, in a pilot study, Kim et al. evaluated the feasibility of IV infusion of up to 2 L of 4°C normal saline by paramedics in the

field after cardiac arrest. The clinical outcomes were promising, showing an effective lowering of the core temperature in patients without any remarkable side effects (Kim et al., 2007). Kollmar et al. (2009) also assessed the impact of infusing 25 mL/kg of ice-cold saline within the first 3 h after AIS. They demonstrated that ice-cold saline might be useful to deliver hypothermia within a neuroprotective treatment window in stroke. Therefore, one could potentially apply a portable ice-cold saline method before arriving at the hospital, where subsequent classical IVC intervention would take place (Harms et al., 2008; Clifton et al., 2011).

Earlier studies expressed that the induction of moderate TH induces the optimal benefit in reducing neurological injury (Maier, 1998; McIntyre et al., 2003). In an experimental study, Kollmar et al. (2007) demonstrated that the greatest histological and functional benefits were achieved with a TT of 35°C. Consistent with this finding, several recent clinical trials also did not report any clinical benefits in cooling their patients to TTs lower than 35°C (Shiozaki et al., 2003; Tokutomi et al., 2009). Furthermore, it seems that the induction of mild TH may produce good clinical outcomes while also minimizing the occurrences of some AEs (Schubert et al., 2008; MacLellan et al., 2009).

In addition to shivering, TH can encounter the patient to a wide range of many other adverse effects including infection, hemodynamic instability, and electrolyte imbalance (Lampe and Becker, 2011). The most common infectious complication is

pneumonia, which happens frequently in proportion to duration and degree of hypothermia (Lampe and Becker, 2011). In patients with space-occupying hemispheric infarction treated with induced hypothermia, pneumonia rates reach up to 83% following cooling induction (van der Worp et al., 2010). To overcome this complication, Harms et al. (2008) have suggested prophylactic antibiotic therapy that can have a considerable impact on the subsequent morbidities and mortalities in TH patients. Hemodynamic AEs following cooling induction includes hypotension, bradycardia, and arrhythmia (Froehler and Ovbiagele, 2010). Among them, bradycardia has been observed in up to 50% of subjects following cooling induction (De Georgia et al., 2004; Froehler and Ovbiagele, 2010). However, it tends to be well tolerated and has not been reported to cause any clinical sequel (Froehler and Ovbiagele, 2010). Furthermore, cooling induction can shift the electrolytes out of the intravascular space, leading to deep hypokalemia, hypomagnesemia, and hypophosphatemia. Opposite electrolyte derangements can also occur during the rewarming phase (Nohl and Jordan, 1986; Turens et al., 1991; Lampe and Becker, 2011). Therefore, for detecting these cooling-induced AEs in the earlier stages, the patient's vital signs, cardiac rhythm, and serum electrolytes levels should be monitored during hypothermic states (Froehler and Ovbiagele, 2010). In the subsequent rewarming phase, most patients have a tendency to become hyperthermic with rebound rises in ICP (Lampe and Becker, 2011). It has been suggested that controlled slow rewarming within 24 h can minimize or prevent rebound rises in ICP and thus associated, subsequent adverse neurological effects (Schwab et al., 2001; McIntyre et al., 2003). It should be mentioned, however, that in the latest guidelines for the management of TBI, a subgroup of analyses did not suggest any clear relationship between cooling durations or rates of rewarming and improved clinical outcomes (Bratton et al., 2007).

We also consider here that careful evidence-based selection of TH candidates will help the ultimate neuroprotective effects to become more apparent in future trials. More specifically, it

appears that patients older than 45 years and those with various co-morbidities have more reported complications and longer hospital stays after induced hypothermia; thus, they may not benefit from this treatment option as much as a younger patient should (Clifton et al., 2001; De Georgia et al., 2004). It has also been shown that TH leads to significantly better clinical outcomes with reduced mortality rates in patients with a GCS of 5 or higher on admission (Marion et al., 1997). In general, promising indicators for successful TH include younger patients and those that have undergone a thorough neurological exam on admission. Furthermore, those patients with TBI who undergo surgical removal of intracranial hematomas should have a better outcome relative to diffuse brain injury cases after hypothermia induction (Clifton et al., 2011). Finally, another group of patients who can benefit from TH are patients with refractory high ICP values. To date, many trials have presented satisfactory effects of TH in reducing ICP in patients who may have suffered a stroke or TBI (Schwab et al., 2001; Sahuquillo et al., 2009). Evidently, clinical trials are currently conducted to better clarify the evidence-based indications (Table 4) to better clarify the evidence-based indications.

The application of TH for other acute neurological injuries such as subarachnoid hemorrhage, spinal cord injury (SCI), and drug resistant epilepsy has been reported (Levi et al., 2009, 2010; Anei et al., 2010; Motamedi et al., 2011), but awaits further study before the routine use can be recommended. In preclinical settings, institution of TH has led to reduced gray and white matter damage and improved motor function in rodent models of SCI (Basso et al., 1996; Yu et al., 2000; Dietrich, 2009). In 2010, attention was brought to a case report of a professional NFL football player who sustained a complete cervical SCI during game-related trauma. The patient received experimental TH along with other routine medical and surgical interventions. The marked neurological improvement in this case made TH a hotly debated topic for management of SCI patients (Cappuccino et al., 2010). A phase I clinical trial evaluated the possibility of applying systemic TH in 14 patients with complete cervical SCI. The clinical outcomes were

**Table 4 | Ongoing clinical trials for evaluating the possible role of therapeutic hypothermia in stroke and TBI\*.**

Study title	Design	Intervention	Target enrollment
Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke	Phase I, randomized, case-control	TH + t-PA	130
The intravascular cooling in the treatment of stroke 2/3 trial	Phase II/III, randomized, case-control	TH + t-PA	400
Mild hypothermia in acute ischemic stroke	Phase II, randomized, case-control	Mild TH	36
Caffeinol hypothermia protocol	Phase I/II, non-randomized, case-control	TH + caffeinol	30
Hypothermia in children after trauma	Phase II, randomized, case-control	Moderate TH	340
Hypothermia in traumatic brain injury in children (HiTBIC)	Phase II/III, randomized, case-control	TH	50
The prophylactic hypothermia trial to lessen traumatic brain injury	Phase III, randomized, case-control	TH	512
Discrete hypothermia in the management of traumatic brain injury	Phase III, randomized, case-control	TH	25
Mild hypothermia and supplemental magnesium sulfate infusion in severe traumatic brain injury (TBI) subjects	Phase II, randomized, case-control	TH + magnesium sulfate	105
Hypothermia in children after trauma	Phase III, randomized, case-control	TH	340
Therapeutic hypothermia for severe traumatic brain injury in Japan	Phase III, randomized, case-control	Mild TH	300

\*Data adapted from [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

promising and the complication rate was similar to normothermic group (Levi et al., 2010). Nevertheless, larger prospective trials for TH in SCI are needed before its routine use can be recommended.

In conclusion, it seems that by determining optimal TH parameters and appropriate clinical applications, cooling therapy has a strong potential to become a valuable neuroprotective intervention in many neurological events. In addition, it is very likely that combining neuroprotective strategies, both invasive and non-invasive, will yield better outcomes than a single approach could. Therefore, the rapid induction of hypothermia to alter deep brain

temperatures seems to be a promising candidate to be a component of multimodal clinical strategies.

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