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Overview of Therapeutic Hypothermia

Shlee S. Song, M.D. and
Cedars-Sinai Medical Center, Department of Neurology, 8730 Alden Drive, Suite E-216, Los Angeles, CA 90048

Patrick D. Lyden, M.D., FAAN, FAHA*
Cedars-Sinai Medical Center, Department of Neurology, 8730 Alden Drive, Suite E-240, Los Angeles, CA 90048

Abstract

Therapeutic Hypothermia has proven neuroprotective effects in global cerebral ischemia. Indications for hypothermia induction include cardiac arrest and neonatal asphyxia. The two general methods of induced hypothermia are either surface cooling or endovascular cooling. Hypothermia should be induced as early as possible to achieve maximum neuroprotection and edema blocking effect. Endovascular cooling has the benefit of shorter time to reach target temperature but catheter insertion requires expertise and training, which may be a barrier to widespread availability. The optimum method of cooling is yet to be determined but a multimodal approach is necessary to address three phases of cooling: induction, maintentance, and re-warm. Specifying core practitioners who are well-versed in established guidelines can help integrate the multidisciplinary team that is needed to successfully implement cooling protocols. Reducing shivering to make heat exchange more efficient with tighter temperature control enables quicker time to target temperature and avoids re-warming which can lead to inadvertent increase in intracranial pressure and cerebral edema. Promising applications but yet to be determined is whether hypothermia treatment can improve outcomes in acute ischemic stroke or traumatic brain injury.

Keywords

Hypothermia; Therapeutic hypothermia; Cardiac arrest; Cerebral ischemia; Surface cooling; Endovascular cooling; Shivering; Neuroprotection; Treatment

Introduction

Therapeutic Hypothermia (TH) improves neurological recovery and reduces mortality after global ischemia, such as in patients with cardiac arrest[1-3], and in infants with moderate or severe hypoxic-ischemic encephalopathy[4]. The therapeutic effects of hypothermia were discussed as early as 400 BC when Hippocrates mentions the use of snow and ice to reduce hemorrhage in patients[5]. The therapeutic implications of hypothermia reentered the modern literature starting in the 1940-50s with the specific use of TH in cardiac arrest patients[6] in

*corresponding author: P: 310-423-5166, F: 310-967-0601patrick.lyden@cshs.org.
P: 310-423-5349, F: 310-248-8038, shlee.song@cshs.org

Disclosure

Drs. Song and Lyden are investigators at Cedars-Sinai for the Intravascular Cooling in the Treatment of Stroke 2/3 Trial (ICTuS2/3). This study is part of the National Institutes of Health–sponsored, Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) program, which allows researchers to enhance and initiate translational research that ultimately will benefit stroke patients by treating more patients in less than 2 hours, and finding ways to treat additional patients later.

1959. Many animal models have shown evidence of reduced histopathology and favorable functional outcomes[7-9]. A recent meta-analysis of randomized controlled trials showed favorable neurologic outcomes for those that received TH, defined as core body temperature less than 35°C within six hours of hospitalization in those who were resuscitated from cardiac arrest[3].

Despite mounting evidence of efficacy and published guidelines supporting the use of TH[10], implementation of hypothermia treatment has been under utilized[11]. Identified barriers to implementation include lack of awareness of effective hypothermia techniques and controversies regarding the best method to reach target temperatures. Specifying core practitioners who are well-versed in established guidelines can help integrate the multidisciplinary team that is needed to successfully implement cooling protocols.

Pathophysiology

The neuroprotection offered by TH has been attributed to reducing cerebral metabolic demmand by decreasing decreasing the rate of oxygen consumption and reducing ATP demand [12]. Halting early gene expression of c-fos and excitatory neurotransmitors plays a central role in preventing neuronal cell death [13]. TH also stabilizes the blood brain barrier and reduces cerebral edema by decreasing permeability to inflammatory cytokines and potential harmful substances such as free radicals[14] and thrombin[15]. Pilot studies in acute cerebral ischemia showed endovascular hypothermia decreased acute cerebral edema using CT imaging parameters[16].

TREATMENT

Cooling Methods

There are multiple issues to consider when inducing hypothermia such as mode of cooling and ease of implementation, patient safety and tolerability, speed of reaching target, duration of cooling, and monitoring for complications. The optimum method of cooling is yet to be determined but a multimodal approach is necessary to address three phases of cooling: induction, maintentance, and re-warm.

In general, two methods of induced hypothermia are used currently: surface cooling and endovascular cooling. Surface cooling methods include convective air blankets, water mattresses, alcohol bathing, cooling jackets, and ice packing. Surface cooling techniques have been used for many years in the treatment of fever. Initial studies of TH in large strokes, cardiac arrest, and the neonatal asphyxia used surface cooling. Patients with these conditions are usually comatose, intubated, and ventilated[17, 18]. The advantages of surface cooling are that it does not require advanced equipment or expertise in catheter placement and avoids the risks associated with central venous catheter placement. External cooling, however, is slower than endovascular cooling and requires the use of sedatives and paralytics to prevent discomfort and shivering in most cases for target temperatures below 35°C[19]. The use of paralytic agents renders accurate physical assessment and detection of neurologic worsening impossible. Cooling of the skin surface induces vasoconstriction and reduces heat exchange in cooled patients; vasoconstriction reduces temperature control, which has lead to target temperature overshoot and lack of control during re-warming[16, 20]. Uncontrolled re-warming has been associated with rebound cerebral edema, elevations in intracranial pressure, and death.

Selective head cooling methods may bypass some of the limitations of systemic cooling[21]. Recent studies using cooling helmets, for example, show promise and easier implementation than systemic cooling methods but required several hours to reach target temperatures[22].

Adding neck cooling may effectively shorten the time required to reach target temperature and cool deep brain structures more effectively than superficial head cooling alone[23]. Newer surface cooling systems, such as energy transferring skin pads may also allow for better temperature control, but this has not been confirmed in controlled clinical trials[24]. Other recent novel approaches include transnasal evaporative cooling, a prehospital technique that allowed cooling treatment to begin in cardiac arrest patients prior to hospital arrival[25]. Treated patients in this trial reached target temperature to 34°C quickly but adverse events included periorbital emphysema, epistaxis, perioral bleeding, and nasal discolorations.

Endovascular cooling using catheters with antithrombotic coatings is feasible and safe[26]. The benefits of this invasive technique includes shorter time to reach target temperature, which can be accomplished within an hour of cooling initiation[27, 28]. An important determinant of efficient cooling was body surface area. Larger patients are more difficult to treat while lighter and older patients were cooled more easily[28]. Catheter insertion requires expertise and training, which may inhibit availability[29]. The catheter attached to a cooling unit comprises an indwelling heat transfer system without requiring cold fluid infusion or extra-corporal heat transfer.[30] Reducing shivering to make heat exchange more efficient with tighter temperature control enables quicker time to target temperature. Precise temperature control avoids overshoot and accidental re-warming, inadvertent increase in intracranial pressure and cerebral edema[31]. Adverse events associated with endovascular cooling include pneumonia, cardiac arrhythmia, thrombocytopenia, and vascular dissection[32].

Tolerability and Control of Shivering

The human thermoregulatory system tightly controls core body temperature near 37°C. Protective mechanisms against hypothermia include muscle shivering and cutaneous vasoconstriction. Cutaneous vasoconstriction reduces heat conduction through the skin; shivering produces energy and heat through repetitive muscle contractions[33]. In addition to substances that alter hypothalamic temperature control, neuromuscular blocking agents are effective against shivering. In the clinical trials of hypothermia in patients after cardiac arrest, neuromuscular blockade was used to prevent and treat shivering[2]. Proper sedation is required in conjunction with paralytics, but monitoring neurologic status is limited during neuromuscular blockade. Shivering in the conscious patient creates discomfort and reduces the effectiveness of cooling. Most patients with large ischemic stroke have a reduced state of consciousness but are not comatose. To assure patient comfort and to cool effectively, shivering must be reduced with centrally active agents. In stroke patients, intubation and paralysis is avoided to minimize the risk of aspiration and pneumonia[28]. In patients who receive endovascular hypothermia, surface skin-warming blankets can reduce the shivering threshold and increase patient tolerability and comfort. Most data concerning shivering controls comes from research to control post-anesthetic shivering. Over 20 clinical trials have shown that meperidine (pethidine), clonidine and doxapram are the most effective drugs to suppress shivering without significant respiratory depression[34]. More recent studies have shown that propofol, buspirone, magnesium, tramadol and dexmedetomidine are effective anti-shivering therapies as well[35]. The significant respiratory depression associated with propofol and dexmedetomidine requires that these are restricted to intubated patients.

Therapeutic Uses

Hypothermia treatment can help provide neuroprotection in cases of anoxic brain injury and global brain ischemia, hence its application in cardiac arrest patients and neonatal hypoxic-ischemic encephalopathy[1, 4]. The treatment effectiveness in other neurological injuries such as stroke and traumatic brain injury is not established firmly[26, 27, 36, 37]. CT and MRI based surrogate markers may aid in the early diagnosis of edema after stroke.[38-40] Hypothermia

should be induced as early as possible to achieve maximum neuroprotection and edema blocking effect[41]. Controversy remains, however, regarding the therapeutic window for hypothermia and the optimum cooling duration. Preclinical studies show hypothermia can reduce infarct size when cooling begins within 3 hours after ischemia[42, 43]. Other reports found that delaying hypothermia for more than 3 hours after ischemia showed no significant neuroprotection,[44] while Colbourne et al. have shown that cooling over 24 hours has neuroprotective effects, even when the treatment was delayed by 6 hours[45].

In regards to cooling duration, animal models suggest longer hypothermia treatment offered better neuroprotection[46]. Shorter periods of cooling suggest only transient neuroprotection. In the gerbil two vessel occlusion model, intra-ischemic hypothermia prevented cell damage in the hippocampus when continued for 4-6 hours, while cooling for 2 hours showed less protection, and cooling for 0.5-1 hour showed no protective effect[44]. The studies with the best long term outcome are those in which hypothermia continues for 24 hours[47]. Longer periods of cooling are reported anecdotally in the treatment of brain edema, but there are no controlled studies. Targeted hypothermia treatment was induced by cerebral microdialysis in patients undergoing continuous intracranial pressure monitoring[48]. Some reports suggest that to reduce cerebral edema, hypothermia duration may be needed for 48 to 72 hours after symptom onset[32]. Longer duration of hypothermia treatment, however, was associated with more adverse effects suggesting treatment should be limited to 24 hours[49].

In the COOL-AID study, a randomized control trial of acute ischemic stroke patients, 18 subjects received intravascular cooling compared to 22 control patients. Results showed less infarct volume growth on imaging in treated patients compared to controls but the clinical outcomes between groups did not differ significantly[27]. In a separate study by Guluma et al, 18 ischemic stroke patients were treated with intravascular cooling. Results showed cerebral edema at 36 to 48 hours was significantly less in the treated group versus the control patients using a validated measure of CSF volume. At 30 days, cerebral edema did not differ between cooled and non-cooled patients and the infarct volume and clinical outcome showed no significant difference[16].

In a randomized, multicenter trial combining IV t-PA with hypothermia, the ICTuS-L trial showed no significant difference in intracerebal hemorrhage rates and mortality rates between cooled and non-cooled patients. There were higher rates of pneumonia in cooled patients but this did not reflect adversely on 3-month clinical outcomes between treated and control patients[50]. The phase III efficacy trial of ICTuS 2/3 is ongoing with a concerted effort to reduce cooling induction time to one hour. The European Hypothermia trial, EuroHyp-1 is also a randomized multicenter study to assess efficacy and safety of hypothermia in ischemic stroke patients (http://www.eurohyp1.eu/). These ongoing trials will help determine strategies for optimal cooling technique and establish whether hypothermia provides favourable outcomes for ischemic stroke patients.

Controversy remains on whether hypothermia can be administered safely and provide neuroprotection in traumatic brain injury. In a systematic review, there were more than 1400 closed traumatic head injury patients in 22 randomized controlled trials using TH[51]. Results show TH reduced mortality rates and unfavourable outcomes such as severe disability or vegetative state. TH however, was associated with higher rates of pneumonia. In an effort to address inconistencies in prior published TH results, a recent multicenter, randomized, double-blind control study aimed to evaluate whether early induction of hypothermia within 2.5 hours of injury provided neuroprotection at 6 month follow-up[52]. The results however did not show significant difference between cooled and non-cooled patients and it remains to be determined which subgroups of traumatic brain injury benefits from TH.

Conclusions

Hypothermia improves neurologic outcome and decreases mortality in patients with global cerebral ischemia, such as cardiac arrest patients and infants with hypoxicischemic encephalopathy. To provide effective treatment, optimal induction and safe rewarming methods need to be determined. Hypothermia has not been proven to show benefit in patients with stroke and traumatic brain injury. Therefore, hypothermia should only be used in randomized controlled trials in this patient population.

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