Therapeutic hypothermia in acute ischemic stroke


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Induced hypothermia has been used for neuroprotection in cardiac and neurovascular procedures. Experimental and translational studies provide evidence for its utility in the treatment of ischemic cerebrovascular disease. Over the past decade, these principles have been applied to the clinical management of acute stroke. Varying induction methods, time windows, clinical indications, and adjuvant therapies have been studied. In this article the authors review the mechanisms and techniques for achieving therapeutic hypothermia in the setting of acute stroke, and they outline pertinent side effects and complications. The manuscript summarizes and examines the relevant clinical trials to date. Despite a reasonable amount of existing data, this review suggests that additional trials are warranted to define the optimal time window, temperature regimen, and precise clinical indications for induction of therapeutic hypothermia in the setting of acute stroke. (DOI: 10.3171/2011.4.FOCUS1154)

Key Words • hypothermia • stroke • brain cooling method • clinical trial • vascular disorders

Therapeutic hypothermia was first described in the Edwin Smith Papyrus, the oldest medical text known to man. History books have since repeatedly documented efficacy in the resuscitation of cold-water drowning victims. In the 1930s, Dr. Temple Fay, an American neurosurgeon, pioneered the use of hypothermia in the treatment of neurological disease. The concept was first applied to patients with intractable pain, and later to intracranial processes such as traumatic brain injury, abscesses, and cerebritis. In the 1950s, hypothermia was effectively used in cardiac arrest victims and during cardiac bypass surgery. Shortly thereafter, the model was applied to intracranial aneurysm surgery, to create a bloodless operative field and allow for controlled tissue dissection. Hypothermic circulatory arrest has since been effectively used to treat complex aneurysms that are not amenable to standard techniques. Half a century later, the medical community demonstrated that therapeutic hypothermia could be used as an effective neuroprotective agent for out-of-hospital cardiac arrest survivors. To date, hypothermia is the only treatment modality proven to have neuroprotective effects in clinical trials of global cerebral ischemia such as cardiac arrest and newborn hypoxic encephalopathy. These findings have generated enthusiasm for the use of hypothermia as a neuroprotectant in focal ischemic stroke. Successful implementation, however, thus far has been marred by clinical trials with small sample size, prolonged time to intervention, and concern for potential side effects. In the following article we explore the current development of hypothermia as a neuroprotectant in acute ischemic stroke. The review focuses on therapeutic delivery methods, mechanisms of action, potential side effects, and complication avoidance, and then examines existing data from clinical trials (means are expressed ± SD throughout).

Pathophysiological Indications

Therapeutic hypothermia is defined as an intentionally induced, controlled reduction of a patient’s core temperature below 36°C. Further classification delineates mild (34°C–35.9°C), moderate (32°C–33.9°C), moderate/deep (30°C–31.9°C), or deep (< 30°C) hypothermia. Ischemia produces variable degrees of tissue damage, with apoptosis and cellular death as the final common pathways of a multifactorial process. Brain tissue ischemia leads to ATP depletion within a very short period of time. The exhaustion of ATP triggers membrane depolarization from an uncontrolled influx of ions in the setting of nonoperational Na+-K+ ATPase pumps. Changes in membrane potentials release EAAs and promote Ca influx. Excess intracellular Ca initiates mitochondrial injury. Affected mitochondria produce oxygen free radicals, and release cytochrome C, causing activation of caspase-mediated DNA fragmentation and cellular apoptosis. If reperfusion occurs, the injured mitochondria may further contribute to neuronal damage. Likewise, an influx of in-
Experimental animal studies have demonstrated that hypothermia effectively targets a multitude of ischemia-induced pathways. These processes, which are invariably detrimental to sustained cellular activity, include energy depletion, ion shifts, free radical formation, EAA release, and inflammation.\(^3,34,47\) Hypothermia reduces cerebral oxygen consumption by a rate of approximately 6% per 1°C change in temperature, allowing preservation of potentially viable brain tissue for longer periods of time.\(^4,9,47\) Lowering brain temperature expedites restoration of ionic homeostasis and impedes ischemia-induced EAA release.\(30,35,41,42\) Furthermore, free radical formation and inflammatory responses are inhibited during hypothermia.\(^11\) Thus, hypothermia counters multiple steps of cellular injury to reduce the recruitment of penumbral tissue into the ischemic core following acute stroke.\(^23\)

### Methods of Cooling

Methods of inducing therapeutic hypothermia may be divided into surface, intravascular (core), and selective types. Numerous surface cooling methods use air, volatile liquids, or cold water and/or ice as thermoconductive media. Surface cooling is noninvasive, inexpensive, and easy to implement. Disadvantages include fluctuations in body temperature and a prolonged time to achieve the temperature goal. Intravascular cooling is administered via infusion of ice-cold fluids, or use of devices such as intravascular catheters (with metal or circulating cold water-filled balloon conductors) with electronic feedback temperature control, peritoneal lavage devices, and extracorporeal circulation. The main advantages of core cooling are shorter time to goal temperature and more precise hypothermic control.\(^15,26,32,39\) In recent years, there has been an increased interest in selective brain cooling for the treatment of ischemic stroke. This concept has led to the invention of 2 devices for implementation. Wang et al.\(^45\) conducted a randomized controlled study on induction of hypothermia by using a cooling helmet. The investigators achieved statistically significant decreases in brain temperature in the treatment group while maintaining selective hypothermia for 48–72 hours. The authors did not encounter any of the significant complications classically associated with systemic hypothermia, and concluded that a cooling helmet was safe for implementation by emergency medical services. The Pre-ROSC (return of spontaneous circulation) IntraNasal Cooling Effectiveness (PRINCE) study evaluated a transnasal evaporative cooling device called RhinoChill in cardiac arrest victims.\(^4\) Two hundred patients in whom cardiac arrest was witnessed were randomized to treatment with intra-arrest cooling or standard care. Time to the target temperature of 34°C was shorter in the treatment group. The significant device-related adverse events included periorbital emphysema (1 patient), epistaxis (3), and perioral bleeding (1).

### Potential Side Effects and/or Complications

Shivering is the most frequently noted side effect of induced hypothermia. Typical methods of controlling shivering include counter-rewarming, meperidine, buspirone, magnesium, benzodiazeprines, opiates, and paralytics. Frequent electrolyte shifts can develop during induction of hypothermia, causing significant hypokalemia, hypomagnesemia, and hypophosphatemia. Opposite electrolyte derangements can occur during the rewarming phase.\(^5,23\) Hyperglycemia has also been described and associated with relative insulin resistance.

Mild to moderate hypothermia can decrease heart rate and cause a reduction in cardiac output by 25%–40%. This effect is counterbalanced by a more significant reduction in metabolic rate, which may produce paradoxical increases in venous oxygen saturation. Contrary to common belief, myocardial contractility may be increased by cold temperatures (35.5°C and below) and induce bradycardia. Cardiac arrhythmias usually develop at temperatures below 30°C, although characteristic electrocardiographic changes (for example, Osborne waves) without clinical consequence can be observed before reaching this threshold. Thrombocytopenia\(^36\) and coagulation abnormalities usually occur at temperatures below 33°C.\(^29,32,43,46\) The most common infectious complication is pneumonia (in up to 50% of cases), and happens frequently in proportion to duration and degree of hypothermia.

### Clinical Trials

In the late 1990s, a prospective, observational analysis of the Copenhagen Stroke Study Registry determined that for each 1°C increase in body temperature at admission following acute stroke, the relative risk of poor outcome rose by 2.2.18,34 Based on these data, Kammersgaard et al.\(^19\) conducted a feasibility and safety trial of hypothermia for stroke patients in 2000. In that study, 17 patients with acute stroke (within 12 hours of symptom onset) were successfully cooled to 35.5°C for 6 hours by using surface cooling techniques; 56 patients were included as controls. The authors concluded that induced hypothermia was not associated with poor outcome, death, or an increased incidence of infectious complications. Shivering was reported as the most common uncomfortable event, and was well controlled by pethidine (meperidine). Encouraging results from this safety and feasibility study prompted trials examining optimal delivery models for, and clinical efficacy of, induced hypothermia (see Table 1).

Schwab et al.\(^37\) reported a temperature gradient (range 1°C–2.1°C) between the core body and brain temperature after severe acute MCA stroke. The authors then evaluated the use of moderate hypothermia (33°C core body temperature) in 25 patients with severe MCA stroke. Cooling was achieved within 14 ± 7 hours after the onset of symptoms by using cooling blankets and cold saline infusions. The purpose of this study was to control ischemic cytotoxic edema by maintaining moderate hypothermia for 48–72 hours. Continuous monitoring of ICP, brain temperature, and cerebral perfusion pressure was performed. During the hypothermia period, ICP was well controlled, although rewarming was associated with rebound intracranial hypertension. The reported survival rate was 56%. This compared favorably with natural his-
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<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Total No. of Patients</th>
<th>Trial Design</th>
<th>Cooling Method</th>
<th>Duration (hrs)</th>
</tr>
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<tbody>
<tr>
<td>Schwab et al., 1998</td>
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<tr>
<td>Kammersgaard et al., 2000</td>
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<td>case-control trial</td>
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<tr>
<td>Krieger et al., 2001</td>
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<td>controlled study</td>
<td>cooling blanket, alcohol, ice water baths</td>
<td>47</td>
</tr>
<tr>
<td>Schwab et al., 2001</td>
<td>50</td>
<td>uncontrolled study</td>
<td>cooling blanket, alcohol, &amp; ice</td>
<td>55</td>
</tr>
<tr>
<td>Zweifler et al., 2003</td>
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<td>pilot study in volunteers</td>
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<tr>
<td>Georgiadis et al., 2001</td>
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<tr>
<td>Guluma et al., 2006</td>
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<td>cooling helmet</td>
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<tr>
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<td>transnasal cooling</td>
<td>NA</td>
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</tbody>
</table>

* Entries are grouped according to cooling method. Abbreviation: NA = not applicable.

In a follow-up trial, Schwab et al.\textsuperscript{36} induced moderate hypothermia in 50 patients with malignant hemispheric infarction. Cooling was initiated within 22 ± 9 hours after the onset of stroke symptoms by using surface methods and cold infusions. The target bladder temperature < 33°C was achieved in 6.5 hours (average) and maintained for 55 hours (range 24–72 hours) with passive rewarming for approximately 17 hours. This trial confirmed the previous observation that intracranial hypertension leading to death most frequently occurred during the rewarming phase, and faster rewarming was associated with a more prominent ICP increase. Although the study was not powered to demonstrate efficacy, it yielded a relatively low mortality rate of 38%. Common complications observed in the trial were thrombocytopenia (70%), bradycardia (62%), and pneumonia (48%).

Georgiadis et al.\textsuperscript{38} showed the feasibility of using an intravascular approach for the treatment of patients with severe acute ischemic stroke. Their protocol achieved rapid cooling rates (1.4 ± 0.6°C/hour), with good temperature control in 6 patients subjected to moderate hypothermia (33.4°C–32.2°C). The design of the intravascular cooling device included 3 balloons perfused with circulating cold saline located near the tip of a central line placed into the inferior vena cava via a femoral approach. The most commonly observed side effects were pneumonia, arterial hypotension, arrhythmia, and thrombocytopenia.

Traditionally it was believed that hypothermia could be applied only to intubated and sedated patients. A study by Zweifler et al.\textsuperscript{49} described a method of mild hypothermia induction (tympanic membrane temperature 34°C–35°C) and maintenance by using a surface cooling device (Arctic Sun Energy Transfer Pads) in healthy, unanesthetized, nonintubated volunteers. Shivering was suppressed with acetaminophen and meperidine. The goal tympanic temperature of 35°C was reached in 90 ± 53 minutes (1.4°C/hour). The most common side effects were nausea, observed in 30% of participants, and elevated systolic blood pressure. Guluma et al.\textsuperscript{16} described a method of hypothermia induction in awake, nonintubated patients in whom an intravascular cooling catheter was used. They were able to cool patients to a target core temperature of 33°C by using a combination of buspirone, meperidine, and cutaneous counter-rewarming with a heating blanket to suppress shivering. Moderate hypothermia was maintained for 24 hours, with controlled rewarming achieved over the ensuing 12 hours. This protocol showed good tolerability, with minimal shivering, no rebound hypothermia, and no oversedation.

At present, alteplase is the only FDA-approved medication for the treatment of acute stroke. The compatibility of potential neuroprotective therapies with thrombolytic agents is therefore critical. Prior to 2001, the safety of hypothermia in stroke patients had been documented, but cooling had not been examined as an adjuvant to alteplase. Much of the concern rested on a theoretical risk of intracerebral hemorrhage, because hypothermia could induce thrombocytopenia and coagulopathy. The COOL AID I trial addressed the safety of administering hypothermia after alteplase thrombolysis in patients with acute ischemic stroke. This study enrolled 19 patients with acute stroke (National Institutes of Health Stroke Scale score of > 15) who received alteplase for thrombolysis. Ten patients were subjected to hypothermia (surface cooling with a cooling blanket and intermittent ice water and whole-body alcohol rubs), and 9 patients served as controls. Hypothermia was implemented within 6.2 ± 1.3 hours of symptom onset. Cooling to a core temperature of 32°C was achieved in 3.5 ± 1.5 hours. Bradycardia (in 5 patients), ventricular ectopy (in 3), hypotension (in 3), melena (in 2), fever after rewarming (in 3), infections (in 4), rapid ventricular rate in a patient with atrial fibrillation.
(in 4), myocardial infarction (in 3), and 3 deaths were reported in the hypothermia group. The patients subjected to hypothermia achieved mean modified Rankin Scale scores of 3.1 ± 2.3 at 3 months, versus 4.2 ± 1.6 in non-hypothermic patients. This trial proved the feasibility and safety of combining thrombolytic therapy and hypothermia in patients with acute ischemic stroke.23

A subsequent 2004 study, COOL AID II, was designed as a multicenter randomized pilot trial to evaluate the feasibility of intravascular cooling in patients with ischemic stroke. Patients were enrolled within 12 hours of symptom onset. The target core temperature of 33°C was achieved faster (77 ± 44 minutes) than in the previous surface cooling study, and maintained for 24 hours. However, only 13 of the 18 patients randomized to hypothermia achieved the target temperature. Clinical outcomes and rates of infectious complications were similar in both groups, although the study was not powered to detect such a difference. This trial further supported the findings of COOL AID I, and suggested that endovascular cooling was feasible in patients with moderate to severe ischemic stroke in the anterior circulation territory.6

Two trials, the Intravascular Cooling for the Treatment of Stroke (ICTuS)24 and the Intravascular Cooling for the Treatment of Stroke—Longer window (ICTuS-L).25 further investigated the feasibility and safety of intravascular cooling. The latter trial included 59 patients divided into 2 cohorts. The first cohort included patients who presented within 3 hours of symptom onset. All patients in this group received the standard dose of intravenous alteplase, and were then randomized to therapeutic hypothermia or standard medical care. The second cohort of patients presented at 3 to 6 hours of onset and was randomized to 4 groups as follows: Group 1, no treatment; Group 2, treatment with alteplase only; Group 3, treatment with hypothermia only; or Group 4, combined therapy. The hypothermia protocol included endovascular cooling for 24 hours and controlled rewarming for 12 hours. Because of technical difficulties, hypothermia was not achieved in 2 of 28 patients randomized to cooling groups. Although the incidence of pneumonia was higher in the hypothermia groups, there were no statistical differences in clinical outcome or death at 3 months among the groups.

Given the high mortality rate associated with large MCA infarctions, Els et al.7 proposed an aggressive strategy for the treatment of patients with such infarctions, in 2006, that combined hypothermia and decompressive hemicraniectomy. Twenty-five patients with malignant ischemic stroke, defined as an infarction of more than two-thirds of one hemisphere, were randomized to treatment with hemicraniectomy alone or a combination of hemicraniectomy and mild hypothermia (35°C). The hemicraniectomy was performed within 15 ± 6 hours of symptom onset, and cooling was started immediately after surgery (using surface or intravascular techniques). The combination therapy group showed a tendency for better clinical outcome as measured by the National Institutes of Health Stroke Scale at 6 months, although the difference did not reach statistical significance (p = 0.08). There was no death associated with hypothermia. The authors attributed this finding to a milder cooling regimen when compared with other studies.

Conclusions

Although there is an increasing body of data supporting the utility of hypothermia in acute stroke, there have been no large-scale randomized studies proving efficacy. Prior investigations have differed with regard to induction methods, target temperature, timing, and adjuvant therapies. Hypothermia remains a promising therapeutic modality. Further trials are needed, however, to define the optimal time window and temperature regimen necessary for maximal treatment efficacy if this technique is to alter the current pattern of acute stroke management in clinical practice.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Author contributions to the study and manuscript preparation include the following. Conception and design: Mack, Groysman, Emanuel. Drafting the article: Groysman. Critically revising the article: all authors.

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Neurosurg Focus / Volume 30 / June 2011
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