

# Therapeutic hypothermia and ischemic stroke: A literature review

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## Abstract

**Background:** Ischemic stroke is the fifth leading cause of death in the US. Clinical techniques aimed at helping to reduce the morbidity associated with stroke have been studied extensively, including therapeutic hypothermia. In this study, the authors review the literature regarding the role of therapeutic hypothermia in ischemic stroke to appreciate the evolution of hypothermia technology over several decades and to critically analyze several early clinical studies to validate its use in ischemic stroke.

**Methods:** A comprehensive literature search was performed using *PubMed* and *Google Scholar* databases. Search terms included “hypothermia and ischemic stroke” and “therapeutic hypothermia.” A comprehensive search of the current clinical trials using *clinicaltrials.gov* was conducted using the keywords “stroke and hypothermia” to evaluate early and ongoing clinical trials utilizing hypothermia in ischemic stroke.

**Results:** A comprehensive review of the evolution of hypothermia in stroke and the current status of this treatment was performed. Clinical studies were critically analyzed to appreciate their strengths and pitfalls. Ongoing and future registered clinical studies were highlighted and analyzed compared to the reported results of previous trials.

**Conclusion:** Although hypothermia has been used for various purposes over several decades, its efficacy in the treatment of ischemic stroke is debatable. Several trials have proven its safety and feasibility; however, more robust, randomized clinical trials with large volumes of patients are needed to fully establish its utility in the clinical setting.

**Key Words:** Endovascular, ischemic stroke, neuroprotection, neurovascular surgery, stroke, therapeutic hypothermia

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## INTRODUCTION

Stroke is a leading cause of disability in most industrialized countries and its economic burden is enormous. The American Heart Association/American Stroke Association currently considers stroke to be the fifth leading cause of death in the US. An estimated 6.6 million Americans over the age of 20 have suffered a stroke. Projections show that, by 2030, an additional 3.4 million people aged  $\geq 18$  years will have had a

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stroke, which is a 20.5% increase in prevalence from 2012.<sup>[41]</sup> Significant advancements have been made in the last few decades that have resulted in improved outcomes. Alteplase is the only US Food and Drug Administration-approved medical treatment for acute ischemic stroke,<sup>[49]</sup> and its use doubled between 2005 and 2009.<sup>[1]</sup> However, only one-third of treated patients recover enough to be significantly free of disability. The recent publications of multiple trials have also shown potential benefit of intra-arterial thrombectomy when done in a timely fashion.<sup>[4,22,32,47]</sup> Similar fast-paced advances in research have not been witnessed in proving the benefit of hypothermia in patients suffering from ischemic stroke, even though the treatment shows promise. In this review, we discuss the historical perspective of therapeutic hypothermia, its mechanism of action, and early clinical trials utilizing hypothermia in ischemic stroke patients.

## METHODS

A comprehensive literature search was performed using both the *PubMed* and *Google Scholar* databases to investigate the mechanism of action of therapeutic hypothermia in early animal studies. Search terms included “hypothermia and ischemic stroke” and “therapeutic hypothermia.” Full text versions of the papers included in the review were obtained and independently reviewed by both authors.

A comprehensive search of the recent and current clinical trials utilizing therapeutic hypothermia was performed through the *clinicaltrials.gov* database. Search terms used included “Stroke and Hypothermia.” Full text versions of the published trials were obtained and independently reviewed by the authors. Studies that were terminated early or aborted were omitted. Non-English articles were omitted for this review. No contact was made with any of the authors of the papers included in this review.

## THERAPEUTIC HYPOTHERMIA—WHERE IT ALL STARTED

Therapeutic hypothermia has been used for several years but there is some hesitation to its clinical adaptation worldwide because of the apparent high risk of complications. Only recently has the medical community begun to realize the benefits of therapeutic hypothermia, and its use is now widely propagated for various purposes.

For several decades, therapeutic hypothermia has been used to provide anesthesia during amputations, to prevent cancer cells from multiplying, and to reduce complications during heart surgery.<sup>[15,38]</sup> The first actual recorded clinical use of therapeutic hypothermia was in 1937, when Fay “cooled” a patient to 32°C for 24 h, in a desperate attempt to prevent cancer cells from further multiplying and progressing at lower temperatures.<sup>[15,16]</sup> In

1941, Smith and Fay reported that induced therapeutic hypothermia improved “the recovery of the conscious state of patients with brain injury,” reporting the findings in a large series of patients with severe head injury.<sup>[10]</sup> In 1953, Bigelow and McBirnie demonstrated the beneficial effects of therapeutic hypothermia for the brain and heart during cardiac surgery in a canine model.<sup>[7]</sup> Neurosurgeons started using hypothermia for traumatic brain and spinal cord injury after the work done by Romsoff *et al.* showed that hypothermia reduced the brain volume, blood flow, and metabolic rate of a normal dog brain.<sup>[45,46]</sup> However, these advancements met hurdles in the shape of numerous complications that followed hypothermia, most notably ventricular fibrillation,<sup>[43]</sup> pulmonary complications,<sup>[51]</sup> acidosis,<sup>[8]</sup> and skin damage.

## THERAPEUTIC HYPOTHERMIA FOR NEUROPROTECTION

Scientists have strived to reduce complication rates related to hypothermia because of the encouraging beneficial effects. Hence, the concept of hypothermia in some way inducing neuroprotection received significant attention in the last several decades, with studies examining this possibility being reported. At present, hypothermia is recognized as perhaps the most robust neuroprotectant in the laboratory to date. However, much of our current knowledge is derived from studies performed on cerebral injury models caused by cardiac arrest rather than stroke. Two large, randomized trials, one from Europe and the other from Australia, are now available that show substantial benefit of mild hypothermia on neurologic outcome after cardiac arrest. The Australian study showed that more patients in the hypothermic group had a favorable outcome compared to the normothermic group (49% vs. 26%;  $P = 0.046$ ).<sup>[6]</sup> Similarly, the European study conducted by The Hypothermia After Cardiac Arrest Study Group demonstrated statistically significant improved outcome of the hypothermic group compared to the normothermic group (55% vs. 39%;  $P = 0.009$ ).<sup>[30]</sup>

The molecular cascades that set in after an ischemic stroke are complex. In the acute stage, the decrease in cerebral blood flow disrupts ionic homeostasis, leading to increased intracellular calcium and release of excitatory neurotransmitters. Intracellular edema also occurs when sodium and chloride flood the postsynaptic cell.<sup>[21]</sup> Accumulating intracellular calcium is sequestered by the mitochondria, which causes mitochondrial dysfunction, leading to free radical production, especially if reperfusion ensues. In the subacute stage, neuronal apoptotic and neuroinflammatory pathways are initiated hours to days after the ischemic onset. Cerebral ischemia leads to oxidative stress, excitotoxicity, and initiation of apoptotic pathways that lead to neuronal death.<sup>[11]</sup> These

post-ischemic effects are exacerbated when the patient's temperature increases by 0.5°C or more above 37°C.<sup>[13]</sup> In addition, it has been noted that the formation of free radicals and release of glutamate into the extracellular space are proportional to the temperature of the ischemic tissue.<sup>[3]</sup> Therefore, decreasing the body temperature will translate into sluggish ATP breakdown, leading to improved molecular homeostasis and the return of acid-base balance to near-physiologic levels.

## HOW DOES HYPOTHERMIA WORK?

Various molecular mechanisms are alleged to be responsible for the beneficial effects of hypothermia in ischemic stroke. Some of the few biological mechanisms responsible for the therapeutic effect of hypothermia include the suppression of dopamine and glutamate release;<sup>[10]</sup> reduction in the number of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-Methyl-D-Aspartate (NMDA) receptors expressed on hippocampal neurons after global ischemia;<sup>[17]</sup> attenuation of neuronal apoptosis and reduced activity of prodeath signaling pathways such as p53;<sup>[31,36]</sup> reduction in the production and activity of some of the most potent proinflammatory mediators implicated in stroke, such as interleukin 1 $\beta$ , tumor necrosis factor  $\alpha$ , interleukin 6,<sup>[20]</sup> matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9;<sup>[23]</sup> and inhibition of nuclear factor  $\kappa$ B.<sup>[24]</sup> Hypothermia has little effect on the core of the infarcted tissue, but acts on the tissue at risk in the penumbra. The penumbra provides an ideal environment for generation of free radicals such as hydroxyl (OH $\cdot$ ), superoxide (O $_2\cdot^-$ ), and hydrogen peroxide (H $_2$ O $_2$ ) that can cause substantial damage to cellular DNA and lipid membranes. Induction of hypothermia might dampen the generation of free radicals and ameliorate their deleterious effects.<sup>[20]</sup> Disruption of the blood-brain barrier (BBB) is a well-known phenomenon that follows ischemic stroke. Several studies have consistently shown that moderate brain hypothermia started soon after ischemic insult results in decreased leakiness of the BBB, hence preventing high concentrations of blood-derived serine proteases and zymogen precursors from entering the brain, which can cause aberrant activation of serine protease signaling with deleterious consequences.<sup>[19,27,28]</sup> Hypothermia—given its multiple synergistic effects on ischemia and reperfusion—has shown great potential to be successful at the clinical level.

## PRECLINICAL ANIMAL STUDIES

The development of relatively simple and reproducible animal models mimicking cerebral ischemia has led to numerous studies investigating the feasibility and efficacy of therapeutic hypothermia. Animal models of focal ischemia usually involve the permanent or reversible

unilateral occlusion (for 1–3 hours) of the middle cerebral artery (MCA).<sup>[9]</sup> Despite major differences across animal studies, which include the model and duration of ischemia (temporary vs. permanent) and timing, duration, and depth of cooling,<sup>[50]</sup> hypothermia has shown favorable effects. However, these protective effects were seen in a more consistent and robust manner in models of temporary MCA occlusion (MCAO) than in permanent MCA occlusion. In their meta-analysis, Van der Woop *et al.* reported a less robust effect of therapeutic hypothermia in the permanent MCAO model than that recorded with the temporary MCAO model,<sup>[34]</sup> whereas other studies showed that therapeutic hypothermia had no positive effect on infarct volume reduction in the permanent MCAO model.<sup>[36,39]</sup> One study model of transient MCAO showed 50% reduction in the size of infarct volume in hypothermic rats when hypothermia was induced 1 h after reperfusion.<sup>[53]</sup> Ridenour *et al.* showed that hypothermia yielded no benefits in animals that underwent permanent MCAO; however, in rats with temporary occlusion, the treatment reduced infarct volume by almost 50%, with a trend toward improved neurological function.<sup>[44]</sup> The effect of delayed intras ischemic and postischemic cooling was also tested in animal models. One study reported that brain cooling to 32°C started at the same time as the 60-min bilateral carotid artery occlusion decreased infarct volume by 75%, whereas delaying cooling for 40 min eliminated protection.<sup>[40]</sup> Studies in animals have also demonstrated that hypothermia could be protective if applied once reperfusion has occurred.<sup>[29,52]</sup>

## HUMAN STUDIES

Numerous human studies have been conducted over the past 2 decades investigating the potential therapeutic effects of hypothermia on neuroprotection and improvement in patient outcomes following both ischemic stroke and ischemic stroke with reperfusion. While numerous studies deserve recognition and mention, here, we discuss only those studies that played an important role in the history of therapeutic hypothermia.

In 1998, Schwab *et al.* published a feasibility and safety study of moderate hypothermia in patients with malignant MCA syndrome. Hypothermia to 33°C was induced within 14 h of stroke onset, and significant reductions in intracranial pressure were noted in all patients.<sup>[48]</sup> In this study, most deaths occurred during the rewarming phase because of a rebound increase in intracranial pressure. This study laid the foundation to the use of therapeutic hypothermia in patients with cerebral edema who do not respond to other medical therapies. The Copenhagen Stroke Study was a small case-control study that was among the very first ones to focus on the use of therapeutic hypothermia for

neuroprotection in awake patients with acute ischemic stroke.<sup>[33]</sup> Patients had to present within 12 h of stroke onset and were cooled for 6 h. However, no difference in outcome or mortality at 6 months was noted.

Krieger *et al.* published the first phase of The Cooling for Acute Ischemic Brain Damage (COOL AID) study. This was a pilot study with an open design where authors attempted to demonstrate the feasibility and safety of hypothermia in patients with acute ischemic stroke. Hypothermia was induced by surface cooling utilizing cooling blankets for 12–72 h in patients presenting within 6 h of symptom onset.<sup>[35]</sup> This trial showed that moderate therapeutic hypothermia in patients with acute ischemic stroke is feasible and can be done safely. The second phase of the COOL AID study was a randomized feasibility pilot trial assessing the safety of endovascular cooling in patients with acute ischemic stroke.<sup>[12]</sup> This study showed that the endovascular approach is a much more expedient way to cool patients than surface cooling. The trial also showed that shivering could be managed effectively with a combination of meperidine, buspirone, and skin warming, without intubation and sedation; however, no difference in outcome was seen between the two groups.

The Intravascular Cooling in the Treatment of Stroke (ICTuS) study was a safety and feasibility trial in which the use of an endovascular cooling system to achieve mild therapeutic hypothermia in awake, acute ischemic stroke patients was assessed; the results were similar to the COOL AID study.<sup>[37]</sup>

The Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L) study conducted in 2010 was a randomized controlled trial that assessed the safety and feasibility of therapeutic hypothermia using an endovascular cooling catheter in acute ischemic stroke patients presenting within 6 h of symptom onset. The study also tested the safety and feasibility of coupling therapeutic hypothermia with intravenous alteplase.<sup>[25]</sup> Patients were randomized into various groups depending on their time of presentation and whether they received alteplase and hypothermic treatments. No differences in mortality or 90-day outcomes were reported; however, the incidence of pneumonia was significantly higher in the therapeutic hypothermia group, most likely due to immune suppression. The Intravascular Cooling in the Treatment of Stroke 2/3 (ICTuS2/3) trial, which was investigating long-term outcomes of patients receiving hypothermia plus thrombolysis versus thrombolysis alone, was terminated in April 2015 and shall resume at a later time.

In an effort to investigate the effects of therapeutic hypothermia in a neurosurgical context, Els *et al.*, in 2006, showed that hemicraniectomy and hypothermia together resulted in better 6-month functional outcomes based on the National Institutes of Health Stroke Scale

(NIHSS) vs. hemicraniectomy alone in ischemic stroke patients with malignant cerebral edema.<sup>[14]</sup> Although the study included only 25 patients, the patients were randomized and no difference in side effects or complications were seen between the two groups.

Recently, Hong *et al.* also showed that 48 h of mild hypothermia and 48 h of rewarming following acute ischemic stroke led to a lower incidence of hemorrhagic transformation, a better outcome measured by the modified Rankin Score, and a lesser degree of malignant cerebral edema.<sup>[26]</sup> This study had a much larger number of patients treated with 75 total participants, which lent stronger credence to its conclusions. Keynote human studies are highlighted in Table 1.

EuroHYP-1, a European, multi-centered, phase III randomized controlled trial is currently recruiting participants in order to assess whether 24 h of induced hypothermia to 34–35°C coupled with best medical management results in a better 3-month functional outcome vs. best medical management alone. The study is estimating its enrollment at 1500 participants, which would be one of the largest randomized controlled trials conducted to date on therapeutic hypothermia.

## CLINICAL APPLICATION OF THERAPEUTIC HYPOTHERMIA

### Timing and optimum temperature parameters

Although the optimum timing and duration of hypothermia in human beings is not clear, most active trials attempt to initiate cooling as close to stroke onset as possible. Different levels of hypothermia are defined; mild (>32°C), moderate (28–32°C), deep (20–28°C), profound (5–20°C), and ultraprofound (<5°C) hypothermia. Although the target temperature for cardiac arrest is 32–34°C, target temperature for neuroprotection is unknown. This question was tested in rats by Kollmar *et al.* who found substantial reduction in the infarct size. Furthermore, improvement in functional outcome was observed in the 33°C and 34°C groups compared with the other temperatures tested.<sup>[34]</sup> It is considered that, in clinical stroke, hypothermia may be a more effective strategy of neuroprotection if applied for a long duration after the ischemic event, however, no consensus has been reached in this matter.

### Devices and techniques

Rapid advancements have been made in this area. Conventional cooling techniques to induce whole body hypothermia include surface cooling using circulating cold water or fanned cold air, alcohol baths, icepacks, cold water gastric, bladder lavage, ice-water immersion, and cooling blankets. However, these techniques consume a significant amount of time to achieve the target temperature. Because of the apparent drawbacks

**Table 1: Clinical trials instituting therapeutic hypothermia**

Investigation	Study design	Number treated	Mean age	Stroke scale/score	Mean temperature	Outcomes	Complications	Cooling mechanism
Copenhagen stroke study, 2000 <sup>[42]</sup>	Case control	17	68.6	Scandinavian stroke scale; 25.8	35.5°C	No difference compared to control	No difference compared to control	Cooling blanket
COOL AID, 2001 <sup>[43]</sup>	Randomized pilot study	19	71.1	NIHSS; 19.8	32°C	No difference compared to control	No difference compared to control	Surface cooling device
COOL AID, 2004 <sup>[44]</sup>	Randomized controlled trial	39	60.9	NIHSS; 18.2	33°C	Endovascular cooling is safe and feasible	No difference compared to control	Endovascular cooling catheter
ICTuS, 2005 <sup>[45]</sup>	Uncontrolled study	12	66.2	NIHSS; not reported	33°C	Endovascular cooling is safe and feasible	Shivering treated pharmacologically	Endovascular cooling catheter
Els, 2006 <sup>[48]</sup>	Randomized controlled trial	25	49	NIHSS; 18	35°C	Better clinical outcome based on NIHSS	Increased catecholamine duration	Endovascular cooling catheter
ICTuS-L, 2010 <sup>[46]</sup>	Randomized controlled trial	58	68.9	NIHSS; 14.3	33.4°C	No difference compared to control	Increased risk of Pneumonia	Endovascular cooling catheter
Hong, 2014 <sup>[47]</sup>	Prospective cohort study	75	64.5	NIHSS; 17 (median)	34.4°C	Decreased cerebral edema and hemorrhagic transformation	No difference compared to control	Endovascular cooling catheter and surface cooling device

of surface cooling methods, investigators have examined alternative cooling techniques including endovascular catheters inserted via the femoral vein in the inferior vena cava. Clinical pilot studies in stroke patients show that these catheters provide rapid and precise temperature control.<sup>[18]</sup> A separate series of randomized clinical trials (Induction of Cooling; iCOOL) are underway where different devices including the Rhinocill, a noninvasive intranasal cooling catheter, are being studied. At present, three iCOOL studies are underway to investigate more rapid means to initiate therapeutic hypothermia for ischemic stroke patients. These studies are comparing the feasibility, safety, and efficacy of such methods to help initiate the therapeutic hypothermia process in the field for patients with stroke or after cardiac arrest.<sup>[42]</sup>

### Complications

Hypothermia is not a complication-free modality. Cardiovascular compromise, including decreased heart rate, myocardial infarctions, other arrhythmias such as atrial fibrillation, and reduced cardiac output, has been recorded in previous hypothermia studies.<sup>[5]</sup> Platelet dysfunction and alterations of coagulation enzyme activity during hypothermia have been recorded.<sup>[2]</sup> Therapeutic hypothermia is also reportedly associated with decreased urine output and can cause metabolic problems such as hypokalaemia. ICTuS-L showed increased incidence of pneumonia in the hypothermic group. While several studies, including the COOL AID II study, have shown no significant difference in serious complications during therapeutic hypothermia, shivering as well as intolerance to induced hypothermia (even mild), have been consistently reported. Cardiogenic shock, pulmonary edema, and deep venous thrombosis have also been reported in hypothermic patients, however, several confounding variables coexist for these complications.

### CONCLUSION

The American Stroke Association is predicting the prevalence of stroke to increase in the coming decades. Interventional techniques such as endovascular clot retrieval for the treatment of acute ischemic stroke have proved to be effective in reducing the morbidity and mortality of stroke. In addition to such practices, a novel technique such as therapeutic hypothermia may be effective in improving patient outcomes. Early clinical trials such as COOL AID and ICTuS have lent support to its safety and feasibility; however, more evidence is needed to help prove its use in clinical practice.

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### Conflicts of interest

There are no conflicts of interest.

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