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Therapeutic Hypothermia in Acute Stroke

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1. Introduction

Stroke is the second most common cause of death and a major cause of serious long-term disability in adults in industrialized countries. Approximately 90% of strokes are ischemic and the rest are hemorrhagic.[1] Unfortunately, few effective treatments can be offered during the acute and subacute phases. Since the introduction of tissue plasminogen activator (tPA) in 1995, there are no other medical treatments for ischemic stroke besides the use of antiplatelets for primary and secondary prevention. Moreover, the clinical treatments for hemorrhagic stroke are also limited.

In ischemic stroke most of therapies aim to recanalize the vessel and restore flow through pharmacological or endovascular treatments. However, another approach to preserve brain tissue is through the interruption of catalytic pathways triggered by ischemia. Rapid restoration of oxygen and glucose by thrombolysis will always provide the most effective neuroprotection, but directly targeting the brain parenchyma to confer neuroprotection may be a viable alternative, particularly in conjunction with thrombolysis. Multiple pharmacological attempts have failed in finding an ideal neuroprotective agent. Over 1000 neuroprotective agents have been tested in basic stroke studies with many showing promise.[2] However, to date no neuroprotective agent has successfully transitioned from bench or animal studies into clinical use. Although cooling may be unable to salvage neural tissue that has irreversibly progressed to infarction, hypothermia minimizes the extent of secondary injury as an acute or subacute treatment strategy. Hypothermia is increasingly being used, especially since therapeutic mild hypothermia has demonstrated to positively influence neurological outcome in humans following acute brain injuries, namely, global ischemic brain injury due to cardiac arrest and hypoxic-ischemic encephalopathy in neonates.[3, 4]

Catalytic cascades are generated in the brain tissue surrounding a blood clot after intracerebral hemorrhage (ICH). Hypothermia may also be used as a neuroprotection

treatment in these circumstances. Hypothermia has the potential to minimize secondary injury resulting from insufficient cerebral perfusion pressure or mechanical compression from herniation by ICH. Hypothermia preserves autoregulation of the cerebral vasculature and reduces cytotoxic edema around the hemorrhagic clot.[5]

2. Pathophysiology of ischemic brain injury

Ischemic brain injury is composed by the initial ischemic cascade and reperfusion injury.[6] During cerebral ischemia, cessation of blood flow and hypoxia trigger a complex set of metabolic and biochemical processes that comprise the ischemic cascade. An initial event in the ischemic cascade is the depletion of adenosine triphosphate (ATP), which is generated by oxygen-dependent phosphorylation in the central nervous system. ATP depletion leads to neurolemma depolarization secondary to derangement of Na^+ and K^+ gradients and, consequently, inappropriate accumulation of intracellular Ca^{2+} resulting from both Ca^{2+} influx and release from intracellular Ca^{2+} stores.[7] Increased intracellular Ca^{2+} concentration causes promiscuous activation of multiple intracellular enzyme systems, including protein kinase C, protein kinase B, calcium/calmodulin-dependent protein kinase II, mitogen-activated protein kinases, and phospholipases A_2 , C, and D. Prolonged elevations in intracellular Ca^{2+} concentration trigger the release of neurotransmitters, which couples with the activation of multiple enzyme systems, inevitably leading to necrotic cell death through membrane dissolution if ischemia continues. In dogs, when ischemic brain is reperfused within 3 to 12 minutes, neuronal ATP production appears to recover rapidly, with replenishment of baseline cellular levels within 6 minutes.[8] However, after 30 minutes of ischemia, the replenishment of ATP to baseline levels takes significantly longer (~36 minutes).[9] Furthermore, even after 3 hours of reperfusion after intracranial thrombus injection, brain ATP levels still may not return to baseline levels.[10] Therefore, timely reperfusion is paramount, and after reperfusion is established, the direct cytotoxic effects of the ischemic cascade likely continue for minutes to hours until cellular ATP levels recover sufficiently.

3. Hypothermia at the cellular level

Hypothermia is neuroprotective through several mechanisms. The effects of hypothermia include a wide range of biological processes which include decreasing excitatory amino acid release, reducing free radical formation, enhancing small ubiquitin-related modifier-related pathways, attenuating protein kinase C activity and slowing cellular metabolism.[11-13] Hypothermia has little effect on the core of infarcted tissue, but acts on tissue at risk in the penumbra by modulating different mechanisms that lead to cellular injury and death.[14] A marked reduction in the metabolic demand of penumbral tissue with induced hypothermia may prevent damage due to oxidative stress and energy failure. Cooling also results in reduced proteolysis and excitotoxic damage caused by glutamate toxicity, and reduction in neuronal calcium influx.[15, 16]

For every 1 °C reduction in brain temperature, the cerebral metabolic rate decreases in 6%.[17] Under stress conditions, hypothermia decreases high energy organic phosphates losses,

slows the rates of metabolite consumption and lactic acid accumulation and reduces cerebral metabolic oxygen consumption, while improving glucose utilization.[11]

Hypothermia not only protects the brain by reducing cerebral metabolism during conditions of reduced substrate and shift to anaerobic glycolysis. Hypothermia also suppresses the accumulation and release of glutamate.[18] ATP loss during ischemia leads to ions flowing down their concentration gradients, and eventual efflux of potassium and influx of sodium and calcium.[19] Calcium influxes lead to direct neurotoxicity as well as extracellular accumulation of glutamate, which are neurotoxic. Experimental studies have shown that mild to moderate hypothermia attenuates the initial and delayed rise of extracellular potassium and prevents intracellular calcium accumulation, thus leading to decreased glutamate efflux and finally neuroprotection.

Numerous studies have shown that hypothermia reduces the generation of reactive oxygen species, decreases brain edema, and prevents blood-brain barrier breakdown.[18] One potential mechanism is that hypothermia inhibits matrix metalloproteinases and preserves basal lamina proteins after stroke.[20-22] Moreover, a clinical study of 10 patients with large strokes who underwent mild hypothermia demonstrated lower levels of matrix metalloproteinase than normothermic patients.[23] Serum metalloproteinases are a good marker of blood-brain barrier breakdown.[20]

Hypothermia has been documented by numerous investigators to alter gene expression normally observed after brain ischemia. Whereas a majority of genes are downregulated by hypothermia, a number of genes are also upregulated. [24] Interestingly, many proinflammatory and proapoptotic genes tend to be downregulated.[25-27] Whereas those genes that contribute to cell survival seem to be upregulated. [28-32]

Additionally, hypothermia has been shown to inhibit activation of the inflammatory transcription factor nuclear factor kappa B via temperature-dependent inhibition of its inhibitor protein's kinase. Other studies indicate that hypothermia has antiapoptotic effects such as reduction of cytochrome C release, and inhibition of caspases and proapoptotic genes.[33-37]

4. Cooling temperatures

Therapeutic hypothermia is defined as an intentionally induced, controlled reduction of a patient's core temperature below 36°C. Further classification includes mild (34°C–35.9°C), moderate (32°C–33.9°C), moderate/deep (30°C–31.9°C), and deep (< 30°C) hypothermia. [38]

In general, hypothermia appears to be effective whether the brain is cooled to 33°C or 28°C, but temperatures on the lower end appeared to be most effective according to a recent meta-analysis of the experimental literature.[39] However, lower temperatures are associated with a higher incidence of complications, require more sedation and sometimes even induction of paralysis accompanied by intubation and ventilatory support.

5. Hypothermia in ischemic stroke

Body temperature is increased in 4% to 25 % of patients with acute ischemic stroke within the first six hours after symptom onset.[40] The pathophysiology of this increase in body temperature is not completely understood. Higher body temperature may be a natural consequence of brain infarction. However, animal studies have suggested that higher body temperatures may increase the damage induced by cerebral ischemia.[41] Observational studies in patients with acute stroke have established the influence of body temperature on the clinical outcome of stroke. For each 1 °C increase in body temperature, the relative risk of poor outcome worsens more than two times.[42] This association may be limited to the first 12 to 24 hours from stroke onset.[42] These studies therefore suggest that control of body temperature and fever prevention may improve functional outcome after stroke.

In a systematic review of animal studies, therapeutic hypothermia reduced infarct size by 44% (95% confidence interval 40 to 47%). The best results were obtained with lower temperatures (≤ 31 °C), when treatment was started before or at the onset of ischemia, and in temporary rather than permanent ischemia models. However, a reduction in infarct volume by about one third was also observed with temperature reduction to 35 °C, with initiation of treatment between 90 and 180 minutes, and in permanent ischemia models.[39] The effects of hypothermia on functional outcome were broadly similar.[39] This suggests that temperature-lowering therapy might be effective for large numbers of patients with ischemic stroke.

6. Human studies of hypothermia in ischemic stroke

Clinical studies of induced hypothermia were conducted on humans based on successful cerebral ischemia animal models. One of the first studies cooled 17 patients with stroke admitted within 12 hours from symptom onset (mean 3.25 hours) for 6 hours.[43] Hypothermia was induced (35.5° C) with cooling blankets and shivering was treated with meperidine. Mortality at 6 months after stroke was 12% in the hypothermia group versus 23% in historical matched-controls. Unfortunately, no benefit in terms of outcome was observed. It has been suggested that a longer hypothermia duration of 48–72 h may be required to reduce the formation of cerebral edema which usually occurs during the first 72-h after symptom onset.

Another study by Keller and collaborators measured the cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption (CMRO₂) in six patients with middle cerebral artery (MCA) strokes treated with hypothermia.[44] Patients were intubated and cooled with cooling blankets for 48 to 96 hours. A total of 19 measurements of CBF and jugular bulb O₂ saturation were performed. This preliminary study suggested that moderate hypothermia (33° C) seems to reduce CBF and CMRO₂ in humans.

A small study evaluated the feasibility of inducing and maintaining moderate hypothermia with the use of endovascular rather than surface cooling.[45] Six patients with severe acute ischemic stroke were treated with moderate hypothermia. The pace of cooling was 1.4 +/-

0.6° C/h, and target temperature was reached after 3 +/- 1 h (range, 2 to 4.5 h). During hypothermia, the maximal temperature observed was 33.4° C, and the minimal temperature was 32.2° C. Every patient developed pneumonia and hypotension. This small study demonstrated that induction and maintenance of hypothermia with an intravenous cooling device was feasible.

Cooling for acute ischemic brain damage (COOL-AID), was one of the first studies to evaluate hypothermia in ischemic stroke after thrombolysis.[46] This was a nonrandomized study that used surface cooling to achieve a cooling temperature of 32 ± 1°C for 12 to 72-h. To prevent shivering, all patients undergoing hypothermia were intubated, sedated, and pharmacologically paralyzed. The study demonstrated that hypothermia is technically feasible and safe for patients with acute ischemic strokes who are undergoing thrombolytic therapy. However, the study was too small (10 patients) to determine any solid conclusions.

A later version of the same study, evaluated an intravascular cooling device in the treatment of stroke through the induction of hypothermia. The second COOL-AID was a randomized controlled study of 40 patients presenting within 12- h of symptom onset. Eighteen patients were cooled and 22 received standard medical management, which included thrombolysis in 13 patients. Shivering was suppressed using a forced-air warming blanket, buspirone and meperidine. Eight patients in the hypothermia group required intubation during their hospitalization, one patient was intubated during the maintenance phase of hypothermia and the other for various reasons not related to cooling. Most patients tolerated hypothermia, and clinical outcomes were similar in both groups although there was a trend of reduced lesion growth on diffusion-weighted imaging in the group treated with hypothermia.[47] Side effects included pneumonia, cardiac arrhythmia, and deep vein thrombosis. The main lessons from these two studies (COOL-AID one and two) were that mild hypothermia can be achieved in awake patients with the appropriate cooling and anti-shivering protocols; and that endovascular cooling achieves target temperature faster than surface cooling.

ICTuS is another nonrandomized clinical trial that cooled 18 acute stroke patients using an endovascular cooling device.[48] Patients were cooled within 12 hours of symptom onset. An anti-shivering regimen with buspirone and meperidine was administered prophylactically. Overall, patients tolerated cooling well and the incidence of cerebral hemorrhage did not increase among patients (n=5) who received intravenous (IV) tPA. This trial confirmed that endovascular cooling with a proactive anti-shivering regimen can be accomplished in awake stroke patients. A later brain CT analysis of patients who were effectively cooled (n=7) versus those who were not (n=11), suggested that endovascular hypothermia decreases acute post-ischemic cerebral edema. [49] At the end of the cooling and rewarming period (36–48 h), patients who were effectively cooled had significantly decreased cerebral edema compared to patients who were either ineffectively cooled or not cooled at all. The effect disappeared by 30 days, as might be expected given the natural course of post-infarction cerebral edema.

A follow-up randomized, controlled study of endovascular cooling in awake patients after stroke (ICTuS-L), studied hypothermia with thrombolysis in patients presenting with acute ischemic stroke < 6 h from symptom onset.[50] Twenty eight patients were randomized to receive hypothermia and 30 to normothermia. There were no differences in outcome or incidence of adverse events comparing patients who were treated with tPA and hypothermia with those who were not cooled. For safety concerns, endovascular hypothermia with placement of the femoral cooling catheter was not begun until 30 to 180 minutes after completion of the tPA infusion, delaying cooling. Pneumonia was more frequent after hypothermia, although the occurrence of pneumonia did not significantly affect outcome at 90 days. The study used meperidine, oral buspirone, and surface skin warming to prevent shivering in awake patients. This study demonstrated the feasibility and preliminary safety of combining endovascular hypothermia after stroke with intravenous thrombolysis, similarly to what the COOL AID study demonstrated previously.[46]

The experience in the use of hypothermia with thrombolysis is limited in stroke patients. In the first COOL-AID study that used surface cooling, 4 of 10 patients received intra-arterial thrombolysis, and 2 received IV therapy.[46] In the second study, 3 of 18 patients were treated with intra-arterial therapy, and 10 received IV thrombolysis.[47] One patient who was treated with hypothermia and intra-arterial thrombolysis experienced retroperitoneal hemorrhage.[47] In the ICTuS-L trial, the rate of ICH was similar among patients who received tPA with hypothermia and those treated with tPA alone.[51]

Hypothermia has also been studied with other neuroprotective agents in the treatment of acute ischemic stroke. Twenty patients with acute ischemic stroke were treated with caffeinol (caffeine 8-9 mg/kg + ethanol 0.4 g/kg intravenously x 2 hours, started by 4 hours after symptom onset) and hypothermia (started by 5 hours and continued for 24 hours (33-35° C), followed by 12 hours of rewarming).[52] IV tPA was given to 16 patients within 3 hours of symptom onset. Meperidine and buspirone were used to suppress shivering. Cooling was successfully achieved in 16 patients via endovascular and surface approaches. All patients reached target temperature, on average within 2 hours and 30 minutes from induction and 6 hours and 21 minutes from symptom onset. Three patients died: one from symptomatic hemorrhage, one from malignant cerebral edema, and one from unrelated medical complications. No adverse events were attributed to caffeinol.

A small study evaluated the use of ice-cold saline for the induction of mild hypothermia in 10 patients with acute ischemic stroke.[53] Ice-cold saline at 4°C (25 mL/kg body weight) was administered one time to induce mild hypothermia. Patients received buspirone and meperidine to prevent and treat shivering. Tympanic temperature dropped significantly by a maximum of $1.6 \pm 0.3^{\circ}\text{C}$ at 52 ± 16 minutes after ice-cold saline was started. The procedure was well tolerated, however, hypothermia was not maintained after the infusion of ice-cold saline.

7. Hypothermia and thrombolysis

Theoretically, the combination of hypothermia with pharmacological thrombolysis to restore blood flow and provide neuroprotection is a very promising strategy. However,

many serine proteases are affected by temperature, and the activity of tPA may be reduced in hypothermia.[54] In vitro analysis shows that cooling to 30°C to 33°C decreases tPA activity by 2% to 4%.[55] Moreover, it has been reported that the response to tPA may be related to body temperature at stroke presentation.[56] Investigators studied 111 acute stroke patients given tPA and found that patients presenting with a higher body temperature were more likely to have a favorable outcome compared with patients presenting with lower body temperatures. The authors suggested that this surprising finding might be explained by the benefit of improved clot lysis by tPA at higher temperatures compared with the potential neuroprotective benefit of lower body temperature.

A recent analysis of 5586 patients with acute ischemic stroke (1980 patients received tPA) determined that tPA treatment effect was not associated with baseline temperature.[57] Point estimates showed benefit of tPA treatment across 35.5°C to 37.5°C but showed a negative trend >37.5°C. Temperature profiles did not influence tPA effectiveness over 72 hours after stroke.

8. Hypothermia in the treatment of large MCA strokes

Hypothermia has also been evaluated in the treatment of cerebral edema after large MCA infarctions. Schwab and collaborators induced moderate hypothermia in 25 patients with large MCA strokes.[58] Hypothermia was induced within 14 ± 7 hours after stroke onset by external cooling with cooling blankets, cold infusions, and cold washing. Hypothermia at 33°C body-core temperature was maintained for 48 to 72 hours, and intracranial pressure (ICP), cerebral perfusion pressure, and brain temperature were continuously monitored. Elevated ICP values were significantly reduced during hypothermia. Herniation caused by a secondary rise in ICP after rewarming was the cause of death in most patients. The most frequent complication of moderate hypothermia was pneumonia in 10 of the 25 patients (40%). Authors concluded that moderate hypothermia can help to control critically elevated ICP values in severe space-occupying edema after MCA stroke. This and a similar study by the same group were pivotal in demonstrating that hypothermia was safe and effective in the treatment of increased ICP after malignant MCA infarction.[59]

A prospective study performed by the same group, induced hypothermia in 50 patients with cooling blankets as well as alcohol and ice bags within 22 ± 9 hours after stroke onset.[59] Hypothermia was maintained for 24 to 72 hours and passive rewarming performed over a mean duration of 17 hours. Time required for cooling to < 33°C varied from 3.5 to 11 hours. The most frequent complications of hypothermic therapy were thrombocytopenia (70%). Faster rewarming (< 16 hours) was associated with rebound increased ICP, and most deaths occurred during the rewarming period. Further data in MCA infarct patients suggests that controlled rewarming rates of ≤ 0.1 per hour allow for improved control of ICP when compared with patients in whom rewarming is achieved in an uncontrolled fashion.[60]

Georgiadis and collaborators compared hypothermia with hemicraniectomy in the treatment of more than 2/3 of the MCA infarction.[61] Seventeen patients underwent hemicraniectomy and 19 were treated with moderate hypothermia (33°C), which was induced with cooling blankets and endovascular devices. Hypothermia was induced for 71 ± 21 hours (range, 24 - 116 hours), whereas duration of rewarming varied between 25 and 34 hours. Prolongation of hypothermia >72 hours was always related to raised ICP during rewarming attempts. Mortality was 12% in the hemicraniectomy group and 47% in the hypothermia group; one patient treated with hypothermia died as a result of cooling complications (sepsis) and three patients died of ICP crises that occurred during rewarming.

Another small prospective study with 25 patients compared hypothermia with hemicraniectomy and hemicraniectomy alone in the treatment of patients with large MCA strokes.[62] Hemicraniectomy was performed within 15 ± 6 h after the ischemic event, followed by hypothermia. There were no severe side effects of hypothermia. Patients treated with hemicraniectomy plus moderate hypothermia had a tendency to better outcome after 6 months when compared to patients treated with hemicraniectomy alone.

9. Human studies of hypothermia in hemorrhagic stroke

ICH accounts for approximately 10% of strokes and the 30-day mortality rate is approximately 52%.[63] After the acute phase of ICH, high morbidity and mortality are essentially caused by the evolution of a peri-hemorrhagic, space-occupying edema associated with gradually increasing ICP.[64] Although the natural course of edema formation is still not fully understood, edema mostly increases during the first week and reaches its maximum during the second week after bleeding onset.[65, 66] Animal studies have suggested that hypothermia may have a neuroprotective role after ICH in reducing edema formation by various mechanisms.[67, 68]

One of the first experiences with hypothermia in the treatment of ICH was reported by Howell and collaborators in 1956.[69] Hypothermia between 30°C to 32°C was induced in eight patients with spontaneous ICH. Although signs of herniation improved in all patients, six patients died from systemic complications, most commonly aspiration. Anecdotally, hypothermia was induced with ice bags, alcohol, and even opening the windows in the middle of the Canadian winter.

Kollmar and collaborators treated twelve patients with supratentorial large ICH (> 25 mL) with hypothermia (35°C) for 10 days.[5] In the hypothermia group, edema volume remained stable during 14 days, whereas edema significantly increased in the control group. However, pneumonia was more frequent in the hypothermia group. Based on these results, the same investigators planned the Cooling in Intracerebral Hemorrhage (CINCH) trial. [70] This is a prospective multicenter trial that WILL enroll 50 patients with large ICH and randomly assign them to mild hypothermia versus conventional medical management.

	Authors	Study	Number of Patients	Time from Stroke	Cooling Technique	Cooling Time	Patient	Anti-shivering	Target Temp	Time to Target Temp	Complications	Comment
Ischemic Stroke	Kammersgaard (43) (2000)	Single center, nonrandomized, open label.	17	12 h	Surface	6 h	Non-intubated	Meperidine	35.5°C	6 h	Infection 18%	Awake patients tolerated surface hypothermia.
	Keller (44) (2000)	Single center, nonrandomized, open label.	6	63.5 h	Surface	48-96 h	Intubated	Midazolam, fentanyl and atracurium.	33°C	NA	NA	Hypothermia decreased CMRO ₂ and CBF.
	Georgiadis (45) (2001)	Single center, nonrandomized, open label.	6	28±17 h	Endovascular	48-72 h	Intubated	Midazolam, fentanyl and atracurium.	33°C	3±1 h	Bradycardia 50% Pneumonia 100% Hypotension 100% Thromb 33%	Induction and maintenance of hypothermia with intravenous cooling was feasible.
	Krieger (46) (2001)	Single center, nonrandomized, open label, parallel control (COOL AID)	10	6 h	Surface	12-72 h	Intubated	Propofol and atracurium.	33°C	3.5±1.5 h	Bradycardia 50% Arrhythmia 30% Hypotension 30%	Hypothermia was well tolerated after thrombolysis.
	De Georgia (47) (2004)	Multicenter, randomized, open label. (COOL AID)	18	12 h	Endovascular	24 h	Non-intubated	Air warming blanket, buspirone and meperidine.	33°C	77±44 min	Pneumonia 11% Arrhythmia 11% Retroperitoneal hematoma 5%	Endovascular hypothermia in awake patients was well tolerated.
	Lyden (48) (2005)	Multicenter, open label, nonrandomized. (ICTuS)	18	12 h	Endovascular	12-24 h	Non-intubated	Air warming blanket, buspirone and meperidine.	33°C	7 h	DVT 22% Bradycardia 22% Hypokalemia 22% Groin hematoma 11% Arrhythmia 11%	Endovascular hypothermia in awake patients was well tolerated.
	Martin-Schild (52) (2009)	Single center, nonrandomized, open label.	18	5 h	Surface and endovascular	24 h	Non-intubated	Air warming blanket, buspirone and meperidine.	33-35°C	8 h	Pneumonia 20%	Hypothermia was combined with caffeine and tPA in nonintubated patients.
	Hemmen (50) (2010)	Multicenter, randomized, double-blinded. (ICTuS-L)	28	6 h	Endovascular	24 h	Non-intubated	Air warming blanket, buspirone and meperidine.	33°C	7 h	Pneumonia 25% DVT 14%	Hypothermia was well tolerated after thrombolysis. 24-h assessments were affected by sedation in the hypothermia group.

Table 1. Main studies of the use of hypothermia in the treatment of acute stroke.

	Authors	Study	Number of Patients	Time from Stroke	Cooling Technique	Cooling Time	Patient	Anti-shivering	Target Temp	Time to Target Temp	Complications	Comment
MCA Stroke	Schwab (58) (1998)	Single center, nonrandomized, open label.	25	14±7 h	Surface	48-72 h	Intubated	Fentanyl, propofol and atracurium.	33°C	14±4 h	Pneumonia 10% Arrhythmia 60%	Hypothermia effective in the treatment of increased ICP after MCA infarction.
	Schwab (59) (1998)	Single center, nonrandomized, open label.	50	22±9 h	Surface	48-72 h	Intubated	Fentanyl, midazolam or propofol and atracurium.	33°C	22 ± 3.5 - 11 h	Thromb 70% Bradycardia 62% Pneumonia 48%	Fast rewarming was associated with rebound increased ICP.
	Georgiadis (61) (2002)	Single center, nonrandomized, open label.	19	24 h	Surface and endovascular	48-72 h	Intubated	Fentanyl, midazolam and atracurium.	33°C	4 ± 1 h	Pneumonia 78% Arrhythmia 42% Bradycardia 58% Thromb 37% Hypokalemia 26%	Hypothermia was compared with hemicraniectomy in the treatment of large MCA strokes. The hypothermia group had higher mortality due to increased ICP during rewarming.
	Els (62) (2006)	Single center, randomized, open label.	12	NA	Surface and endovascular	48 h	Intubated	Fentanyl and midazolam.	35°C	2 ± 1 h	Bradycardia 8%	Hypothermia was used with hemicraniectomy.
Hemorrhagic Stroke	Kollmar (70) (2010)	Single center, nonrandomized, open label.	12	12 h	Endovascular	10 d	Intubated	Sufentanyl, midazolam, meperidine and cisatracurium	35°C	NA	Pneumonia 100% Thromb 33% Bradycardia 25%	Hypothermia decreased perihematomal edema.

Temp = temperature; thromb = thrombocytopenia; CMRO₂ = Cerebral metabolic rate of oxygen; CBF = cerebral blood flow; tPA = tissue plasminogen activator; ICP = intracranial pressure; MCA = middle cerebral artery; NA = not available; h = hour, d = day; min = minutes.

Hypothermia has also been evaluated in the management of subarachnoid hemorrhage (SAH). Gasser and collaborators treated 21 patients with poor grade SAH and cerebral edema with long-term hypothermia (>72 hrs).[71] Nine patients were treated for <72 hrs and 12 for >72 hrs. Functional independence at 3 months was achieved in 48% of patients, but the outcome did not differ with the group of patients treated without hypothermia. The most common form of complication was infection in both groups.

10. Complications of hypothermia

Induced therapeutic hypothermia is an intensive care procedure that has to be performed under continuous monitoring. Since most patients who are cooled are critically ill, they may be more prone to develop complications. These complications appear to be associated with the degree of hypothermia, with the risk of side effects being correlated with prolonged hypothermia and lower temperatures. In general, hypothermia is well tolerated, but complications may include: 1) cardiac: arrhythmias, bradycardia, reduced ventricular contractility, and hypotension; 2) immunologic: immunosuppression; 3) hematologic: thrombocytopenia and mild coagulopathy; and 4) metabolic: shivering, hyperglycemia, hypokalemia, ileus, and cold-induced diuresis. The most common complication in reported studies is pneumonia, followed by asymptomatic bradycardia, cardiac arrhythmias and thrombocytopenia (table).[14]

Pneumonia appears to occur more frequently in intubated patients who undergo cooling. Endovascular cooling with use of warm blankets to reduce shivering and prevent intubation is an alternative to surface cooling and may reduce the rate of pneumonia.

The most dangerous phase of induced hypothermia is the rewarming period. Particular care is required in stroke patients with intracranial mass effect and elevated ICP. Overly rapid rewarming can lead to a systemic inflammatory response syndrome; with systemic vasodilatation, hypotension, and reflex ICP elevation.[14] As a general rule, hypothermia patients with increased ICP should undergo active controlled rewarming (or “decooling”) at a rate of 0.1°C per hour. Faster rates of 0.25°C to 0.33°C per hour can be tolerated in patients without ICP issues.[72-74] This high ICP rebound has especially been observed in patients with malignant MCA infarctions.[75]

One common complication of hypothermia that usually is overlooked is sedation. It has been demonstrated that patients who undergo hypothermia are more likely to receive sedation than those who are not treated with hypothermia.[76] Sedation in hypothermia patients may linger longer in the system, confounding neurological examination and prognostication.[77] This becomes a relevant issue in stroke patients who require daily neurological assessments.

11. Conclusion and recommendations

Despite the many potential neuroprotective effects of hypothermia seen in animal stroke models and the benefit of hypothermia observed in humans following cardiac arrest, there is

still no solid evidence demonstrating improved outcomes in stroke patients. In addition, a systematic review found no definitive evidence that either physical or chemical cooling interventions improve outcomes after acute ischemic stroke.[78] The total number of participants included in the studies reviewed in this chapter is far too small and the interventions too heterogeneous for definitive conclusions (table). Moreover, all studies were designed to test safety and feasibility, and allowed rather long time periods between stroke onset and start of cooling, which may lower the likelihood of observing a treatment effect.

Stroke studies have used surface and endovascular cooling systems for induction and maintenance of hypothermia (table). Goal temperatures usually range from 33° to 35°C. IV infusion of ice-cold saline [25 mL/kg body weight) has been shown to induce hypothermia rapidly and may be used as an initial cooling method in stroke patients who are initially assessed in the field.[53]

Pharmacologic agents like meperidine and buspirone, and concurrent skin warming inhibit shivering and allow patients to tolerate treatment with less sedation. Moreover, these anti-shivering protocols have allowed the induction and maintenance of mild and moderate hypothermia in awake patients.[47] Recent studies have demonstrated that endovascular cooling is more accurate in keeping patients in the target temperature range than surface cooling with ice bags and cooling blankets.[79, 80] Endovascular cooling also allows for concurrent use of surface warming to reduce shivering. However, endovascular cooling implies accessing the femoral vein to place the cooling catheter, increasing the risk of procedural complications and infection. In general, each center should choose the cooling method that is more familiar to the personnel and easier to implement.

Similar uncertainty exists on the optimal treatment duration. In animal models of focal cerebral ischemia, pathophysiological processes exert their deleterious effects over various time courses, extending from the first hours to several days after vessel occlusion.[81] Such observations may imply that temperature lowering therapy should be more effective when used for prolonged time. On the other hand, longer treatment was not associated with improved outcomes in a meta-analysis of hypothermia in animal models of focal cerebral ischemia. Moreover, the risk of side effects such as infections may increase with longer cooling times.[39] In clinical trials of cardiac arrest, hypothermia was maintained for 12 or 24 hours.[3] Most recent studies of hypothermia in acute ischemic stroke aim for 12 – 24 hours of cooling (table).

For unknown reasons, patients with massive brain injuries may experience rebound intracranial hypertension when rapidly rewarmed after prolonged periods of mild to moderate hypothermia. Whether this occurs in experimental stroke models has not been widely studied. Previous stroke studies suggest that controlled rewarming seems to prevent rebound brain edema and is the standard protocol in most recent trials.[14] Trials using milder hypothermia [35°C) and slower rewarming periods have reported lower complication rates.[62] For practical purposes, a 24-hour cooling period followed by a >12-hour slow rewarming, such as 0.1° C/h is advised.[82]

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