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Induced Hypothermia for Acute Stroke

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Abstract-Induced hypothermia is one of the most promising neuroprotective therapies. Technological limitations and homeostatic mechanisms that maintain core body temperature have impeded the clinical use of hypothermia. Recent advances in intravascular cooling catheters and successful trials of hypothermia for cardiac arrest and neonatal asphyxia renewed interest in hypothermia for stroke, resulting in early phase clinical trials and plans for further development. This review elaborates on the clinical implications of hypothermia research in stroke and technical and logistical issues associated with the application of hypothermia. *(Stroke.* 2007;38[part 2]:794-799.)

Key Words: acute care - hypothermia -

neuroprotection

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he Stroke Therapy Academic fudustry Roundtable (ST AIR) criteria have been proposed to assess different neuropro

tective strategies for viability and promise in clinical application.[1] Hypothermia is one of the best studied and most highly effective modes of neuroprotection.[2]

Hypothermia has neuroprotective effects in animal models of brain[3] and myocardial[4] ischemia. In recent reviews of preclinicalliterature, hypothermia was one of the most promising neuroprotective approaches studied.[2] In adult patients, hypothermia improves neurological outcome in survivors of cardiac arrest,[5,6] and its use after cardiac arrest is recommended by the International Liaison Committee on Resuscitation (ILCOR).[7] The use of hypothermia in patients with ischemic heart injury is currently under evaluation.[S] In infants with hypoxic-ischemic encephalopathy, hypothermia of 33.5°C for 72 hours was safe, reduced fatality, and improved neurodevelopmental outcome.[9]

The Cooling for Acute Ischemic Brain Damage (COOL-AlD) study group completed 2 clinical trials of hypothermia in acute ischemic stroke. The fust study used surface cooling,[10] and the second used endovascular cooling.[ll] Both trials demonstrated feasibility but were not powered to answer questions regarding safety and efficacy.

The futravascular Cooling in the Treatment of StrokeLonger tPA Window (ICTuS-L)[12] study is currently under way and aims to test the combination of intravenous tissue plasminogen activator (tPA) and hypothermia. ICTuS-L is a phase I safety study, and it is hoped that it willlay ground for larger phase 11 and III projects. Other clinical studies in ischemic stroke induce mild hypothermia through surface cooling (Controlled Hypothermia in Large Infarction [CHILp3] and Nordic Cooling Stroke Study [NOCSS14]) or combined cytoprotection with hypothermia plus tP A, caf

feine, and ethanol.[15] Details about these studies have not been published.

Thus far, the Cochrane Database shows no completed, prospective, randomized, controlled trial of hypothermia in stroke patients.[16] The 2005 Guidelines on Acute Stroke Treatment by the American Stroke Association find hypothermia after stroke a promising field of future research.[17]

Background

The potential for neuroprotection of hypothermia has long been suspected. Victims of near-drowning in ice-cold water can have a remarkable neurological recovery even after prolonged cerebral ischemia.[1S] Although hypothermia has limited neuroprotective effects in animal models of permanent focal ischemia,[19] models of temporary ischemia show a reduction in infarct size and improvement in behavioral outcome.[20,21]

fu models of global ischemia, the effect of hypothermia depends to a great extent on ischemia duration and time between ischemia and onset of hypothermia. Ikonomidou et a)[22] demonstrated that hypothermia initiated 5 minutes after transient global ischemia protected cortical and hippocampal neurons. Hypothermia initiated 30 minutes after ischemia was not effective. Dietrich et al[23] showed that hypothermia demonstrated the greatest benefits when initiated during global ischemia, whereas hypothermia initiated after global ischemia was not

effective. Furthermore, when hypothermia is begun before ischemia, histological damage can be blocked completely.24

The precise mode of neuroprotective action in hypothermia is not known. Krieger and Yenari25 (2004) reviewed the variety of animal models of hypothermia in stroke. Most likely, hypothermia exhibits multiple and synergistic effects on brain metabolism. Hypothermia decreases the cerebral metabolic rates of glucose and oxygen and slows A TP

breakdown.26 In the range of *22°C* to *37°C,* brain oxygen consumption is reduced by =5% for every degree fall in body temperature.27 Hypothermia reduces glutamate release,28 inflammation, and free radical generation. It lowers metabolic rate, limits edema formation, and interrupts necrosis/apoptoSiS.29.30 In addition, hypothermia reduces intracellular calcium rises after ischemia; the mechanism of this effect is not clear. Hypothermia may impair glutamate-mediated calcium influx or directly inhibit calcium-mediated effects on calciumlcalmodulin kinase.31.32

Hypothermia has significant effects on the production of hydroxyl radicals and suppresses nitric oxide and peroxynitrite formation. Additionally, granulocyte and intercellular adhesion molecule-l upregulation in response to ischemia is attenuated.33 Wang et ap4 showed that inflammatory responses are suppressed as late as 1 week after 2 hours of hypothermia.

In summary, hypothermia may reduce damage from excitotoxins, inflammation, free radicals, and necrosis. This could lead to longer neuronal survival and improved outcome after restoration of blood flow through revascularization methods such as thrombolysis. It mayaiso reduce edema after ischemia and lower the risk of postischemic hemorrhage.3S

Target Temperature

Animal models of transient and permanent cerebral ischemia have used temperatures from *24°C* to *33°C.2S* Although infarct size was reduced in most models, animals with moderate hypotherrnia experienced greater recovery than those with severe hypotherrnia.36 This may be caused by a reduction of regional cerebral blood flow at very low temperatures.37

Terms used to describe hypothermia are not clearly defined. Most consider severe hypothermia as temperature below *28°C,* moderate as *28°C* to *34°C,* and mild as *34°C* to *36°C.* 35 Severe hypothermia was never tested in stroke patients because medical complications of temperatures below *28°C* such as severe hypokalemia, arrhythmia, infections, hypothyroidism, and heart failure in an elderly stroke population make severe hypothermia impractical. Moderate hypothermia was used after cardiac arrest in both the study of Bernard et alS and the Hypothermia After Cardiac Arrest study,6 in neonatal asphyxia in the National Institute of Child Health and Human Development (NICHD) study,9 and for stroke patients in the COOL-AID pilot studies.IO,l1 The ICTUS and ICTUS-L studies use moderate hypothermia to *33°C* but avoid endotracheal intubation by using a novel antishivering protocol.38 Mild hypothermia of *35.5°C* was induced via cooling blankets in a small Danish study of stroke patients39 and via a cooling heimet in aseries of stroke and traumatic brain injury patients in Illinois.40

Although hypotherrnia below *35°C* is still being investigated in stroke, avoiding fever41.42 and controlling temperature below *36.5°C* have proven to correlate with good clinical outcome after stroke.43.44 The 2003 Guidelines for the Early Management of Patient With Ischemic Stroke by the American Stroke Association include the recommendation to treat sources of fever and to use antipyretics for temperature control in the setting of acute stroke.4S

Surface Versus Endovascular Cooling

Surface cooling methods include convective air blankets, water mattresses, alcohol bathing, cooling jackets, and ice packing. These methods have been used for many years in the treatment of fever and earlier studies of neuroprotection. Both cardiac arrest and the neonatal asphyxia study used such techniques. Patients in these conditions, however, are usually comatose and endotracheally intubated and ventilated. Patients who are on

arespirator can be heavily sedated and paralyzed, effectively negating shivering and discomfort, which might otherwise interfere with therapy. In the first COOL-AID study, which used surface cooling,lO all patients were intubated, as were patients treated by Schwab et al46 for herniation after large middle cerebral artery stroke. Only a minority of stroke patients, however, require endotracheal intubation. Any successful application of hypothermia in the majority of moderate or severely affected stroke patients would be practical only if intubation was not needed in the treatment course.38

Advantages of surface cooling are that it does not require advanced equipment or expertise in catheter placement and averts the risk associated with central venous catheter placement. Cooling through external methods, however, requires many hours to reach and maintain a temperature below *35°C* and, in most cases, necessitates the use of sedatives and paralytics to prevent discomfort and shivering. Using paralysis and sedation requires endotracheal intubation and ventilation, which in turn are associated with significant risks of ventilator-associated pneumonia and other complications. Patients under paralytics render neurological assessments and detection of neurological worsening during the cooling period virtually impossible. In addition, cooling of the skin leads to vasoconstriction and reduces the heat exchange in cooled patients, which makes temperature control very difficult. This may lead to target temperature overshoot (COOL-AID I) and lack of control during passive rewarrning, which may be associated with reactive brain edema.10

In patients who are awake, surface cooling is only achieved as an approach for mild hypothermia and fever control. New surface cooling devices, such as energy-transferring skin pads,47 may demonstrate areduction in the time to target temperature and allow better temperature control.48

Endovascular cooling has become feasible via newly developed catheters with antithrombotic coverings that can be inserted into the central venous system and allow cooling via indwelling heat transfer devices. Prior attempts at endovascular cooling were limited by the need to infuse large volumes of chilled saline49 or caused thrombotic complications surrounding the heat exchange device. The new devices exchange heat via transduction through internal circulation within the catheter; no fluid enters the patient. *so* Thrombotic complications are reduced with the use of the antithromboticeluting catheter.

Endovascular cooling allows rapid heat exchange and faster cooling toward target temperature. Shivering is in part driven through skin receptors. Endovascular cooling allows skin warming during cooling and, in turn, reduces shivering to make heat exchange more efficient and temperature control tighter. This avoids target temperature overshoot and inciden
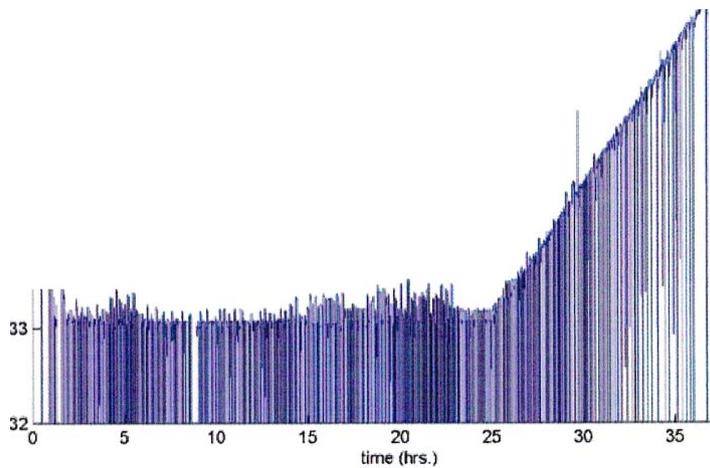
Representation of core venous temperature during endovascular hypothermia with the use of a 14F intravenous heat exchanger (Celsius Control System, Innercool Therapies, San Diego, Calif) in the ICTuS-L trial.

tal rewanning, which can lead to increases in brain edema and intracranial press ure (Figure).

in 2 models when delayed by up to 6 or 3 hours.57 Two hours of cooling was only effective when initiated within 2 hours, implying a shorter time window for brief hypothermia.58

Treatment Window and Duration

In animal studies, hypothermia during ischemia abolished the ischemic damage completely, and hypothermia within 3 hours significantly reduced infarct size.51.52 Some reports found that delaying hypothermia for > 3 hours after ischemia showed no significant neuroprotection,23 whereas Colboume and Corbett53 have shown that cooling over 24 hours has neuroprotective effects, even when the treatment was delayed by 6 hours. Arecent study in fetal sheep confmned the neuroprotective effect of delayed hypothermia. In this model of 72 hours of brain cooling, hypothermia was initiated with a 2- or 6-hour delay and compared with sham-operated animals. Both the 6- and 2-hour treatment delay groups showed significant neuroprotective effects.54 This long ther-apeutic window is very promising because patients often present to the emergency departrnent with a delay of a few hours after stroke onset.

The duration of cooling with best neuroprotective effects is not known. Yanamoto et al55 compared cooling for 22 and 3 hours after transient middle cerebral artery occIusion. Animals in the 22-hour group had better neuroprotection. In the gerbil 2-vessel occIusion model, intraischemic hypothermia completely prevented hippocampal cell damage when continued for 4 to 6 hours, cooling for 2 hours showed less of a protective effect, and 0.5 to I hour showed no protective effect.23 In addition, shorter periods of cooling may lead to only transient neuroprotection. In many experimental models, the animals are euthanized within a few days and potentially miss late neuronal cell death after hypothermia. The studies with the best long-term outcome involved treatment for 24 hours with hypothermia.56

Treatment duration and time window may be interdependent because 24 hours of cooling prevented neuronal damage

Temperature Control and Shivering

The thermoregulatory system tightly controls core body temperature near 37°C. Defenses against cooling incIude shivering and cutaneus vasoconstriction. Cutaneus vasoconstriction reduces heat conduction through the skin; shivering produces energy and heat through repetitive muscIe contractions.59 Shivering is the only heat-producing mechanism in humans and is the main factor in combating hypothermia.

To effectively cool patients and to avoid discomfort, shivering must be avoided. Shivering can be reduced with centrally active substances that alter hypothalamic thermoregulatory centers via skin wanning, which reduces the trigger of shivering through skin temperature sensors and through muscIe relaxation. Most anesthetics and narcotics change thermoregulatory control, and in general the effect on thermoregulatory mechanisms is

proportionate to their anesthetic properties. Most drugs that effectively control shivering therefore lead to either sedation or respiratory depression.60

Meperidine is the most important and cIinically relevant drug that inhibits thermoregulatory responses.61.62 The antishivering action of meperidine decreases the shivering threshold twice as fast as the vasoconstriction threshold and can be achieved at blood levels that do not lead to severe respiratory depression or sedation. A low dose of meperidine (25 mg IV), which does not affect alertness or respiratory function, decreases the shivering threshold by 2°C.63

Mokhtarani et al64 showed a synergistic effect of buspirone and meperidine. Buspirone reduces the shivering threshold to 35.0:t0.8°C, high-dose meperidine reduces the threshold to 33.4:t0.3°C, and the combination of buspirone and low-dose meperidine reduces the shivering threshold to 33.4:t0.7°C.64 The combination did not cause sedation or respiratory de

pression. The mechanism of this synergistic effect is unknown. In patients who are awake, the use of buspirone and meperidine in conjunction with skin warming aIlows cooling to 33°C.

reducing the shivering threshold in men.72 The combination of hypothermia, caffeine, and alcohol is currently being tested in Houston.15

Thrombolysis and Hypothermia

Hypothermia was most effective in preclinical models of transient ischernia.2o Combining hypothermia with therapies to restore blood flow, such as thrombolysis, may be the most prornising strategy to use hypothermia in humans.35

However, many serine proteases are affected by temperature, and the activity of tP A may be reduced in hypothermia. In vitro analysis shows that cooling to 30°C to 33°C decreases tPA activity by 2% to 4%.65 Wolberg et al reported that tPA activity declined to 50% when the clot temperature decreased from 40°C to 30°C. Whereas thrombolysis is reduced by low temperature, other aspects of coagulation and platelet function are also affected by hypothermia. Platelet function deceases when temperature is lowered from 37°C to 33°C,66 and in trauma patients platelet function and coagulation activity are decreased at temperature below 34°C.67

The experience regarding safety and efficacy of thrombolytic use and hypothermia is lirnited in stroke patients. In the first COOL-AID study that used surface cooling, 4 of 10 patients received intra-arterial thrombolysis, and 2 received intravenous therapy.lO In the second study, 3 of 18 were treated with intra-arterial therapy, and 10 received intravenous thrombolysis.ll One patient who was treated with hypothermia and intra-arterial thrombolysis experienced retroperitoneal hemorrhage.l1

The data available thus far are insufficient to address the effect of hypothermia on tP A activity and the resulting safety. The ICTuS-L study will provide further feasibility and early safety data regarding the use of thrombolysis in stroke patients treated with hypothermia, with the use of state of the art endovascular heat exchangers and intravenous tPA.38

Whether hypothermia affects hemorrhagic complications after stroke is unknown. One could hypothesize opposite effects. On the one hand, cooling may reduce hemorrhage after stroke by reducing the activities of matrix metaIloproteinases after ischernia.68 On the other hand, cooling rnight reduce the activity of the recombinant tP A inhibitors, such as plasminogen activator-l, sufficiently that the lytic effect of recombinant tP A is enhanced, resulting in more hemorrhages. Again, trials such as ICTsS-L will begin to generate data on this point.

Combination Therapy With Other Neuroprotective Agents

The possibility of combining neuroprotective strategies was reviewed recently.69 Over the last decades, many neuroprotective trials were undertaken and failed to prove clinical benefit in patients after stroke.70 It is possible that compounds failing to protect when used alone might interact synergisticaIly with other treatments to produce a more effective neuroprotective strategy. Hypothermia is an ideal addition to neuroprotective compounds. In animal models, the combination of hypothermia with tirilazad and magnesium was neuroprotective.71 Magnesium mayaiso have a minor role in

Conclusions

Hypothermia is one of the most prornising neuroprotective therapies yet identified in preclinical studies. Until recently, its use in unanesthetized patients after stroke was not feasible. The development of safer endovascular heat exchangers and novel antishivering protocols, which avoid sedation, makes the routine clinical use of hypothermia after stroke practical. Future studies will need to investigate the effect of hypotherrnia on clinical

outcome, the safety in combination with thrombolysis, and its potential use in conjunction with other neuroprotective strategies.

Disclosures
None.

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