

MILD HYPOTHERMIA IN ACUTE ISCHEMIC STROKE AFTER THROMBOLYTIC THERAPY: A PROSPECTIVE, OPEN, RANDOMIZED, SINGLE- CENTER, SAFETY AND FEASIBILITY STUDY

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SUBJECTS: Adult male and female patients, 18- 85 years of age presenting with symptoms of acute ischemic hemispheric stroke within 6 hours of symptom onset, treated with Actilyse-thrombolysis and with a persisting significant neurological deficit, NIHSS 7-20 (immediately after thrombolysis).

STUDY OBJECTIVES: To provide initial safety and feasibility data regarding mild hypothermia in an acute ischemic stroke patient population using non-invasive temperature management system.

1. Primary endpoint: proportion of patients who maintain temperature of $< 36,0^{\circ}\text{C}$ 80% of the 12- hour study period.
2. Safety objectives
 - a. Compare hypothermia and standard care with regard to the incidence of fatal intracerebral hemorrhage (ICH), nonfatal symptomatic hemorrhage, infections, hemodynamically significant cardiac arrhythmias, severe disturbance of electrolytes and fluid balance, thrombocytopenia, and/or serious adverse events until discharge or 14 days whichever comes earlier.
 - b. All- cause mortality during acute phase (7 days), 1 month, and 3 months follow-up.
 - c. Readmission to hospital for any reason within the 3- month follow-up period.
3. Feasibility objectives
 - a. Assess tolerance to and effectiveness of the shivering suppression protocol and the effectiveness of non- invasive temperature management system in non- intubated patients in achieving and maintaining the desired temperature profile.
 - b. Assess the feasibility of non- invasive temperature management system in acute stroke unit environment.
4. Efficacy objectives
 - a. Compare hypothermia- treated and no-hypothermia treated patients with regard to functional outcome, as measured by the proportion of modified Rankin scale (mRS) responders at 3 months. An mRS- responder is defined as a subject with mRS 0-2 at 3 months.
 - b. Compare hypothermia and no- hypothermia with regard to BI, NIHSS, GOS, size of infarction in MRI, the rate and extent of hemorrhagic transformation in brain parenchyma and the neuropsychological outcome at 3 months.

ABSTRACT

Ischemic stroke is a major cause of mortality and morbidity with limited therapeutic options. Only thrombolysis within 3 h of symptom onset and stroke unit care have shown to improve outcome. As only a fraction of patients receive thrombolysis and not all benefit from it, we are seeking for adjuvant therapies. Hypothermia has been found beneficial in numerous preclinical studies in focal ischemic models and recently in multicenter clinical trials in resuscitated patients with ventricular fibrillation or cardiac arrest. Moreover, hyperthermia frequently complicates stroke and significantly jeopardizes outcome. Since deep hypothermia with invasive cooling procedures necessitate intensive care and, therefore, requires enormous resources and is potentially complicated with adverse events, we aim to imply mild hypothermia (n=18) in awake patients immediately after thrombolytic therapy and compare the results to those of a control group receiving thrombolysis but not hypothermia (n=18), all treated in a stroke unit. The study will take place on the premises of Dept of Neurology, HUCH. This study is designed as a safety and feasibility study to pave the way for larger, multicenter efficacy trials.

BACKGROUND

Stroke is the second leading cause of death worldwide [1]. Approximately 90% of strokes are ischemic in nature [2]. The results of the National Institutes of Neurological Disorders and Stroke Trial showed that patients receiving intravenous tissue plasminogen activator (tPA) within 3 hours of symptom onset were significantly more likely to have an improved outcome at 90-days follow-up [3]. Recanalization of the occluded artery is clearly linked to improved clinical outcome [4]. However approximately half of the patients do not recanalize after administration of tPA [6].

Following arterial occlusion, two factors determine tissue outcome: regional residual cerebral blood flow (CBF) and duration of vessel occlusion. Depending on the severity and duration of hypoperfusion, the tissue supplied by the occluded artery is compartmentalized into areas of brain tissue irreversibly damaged, and areas of brain tissue hypoperfused but viable. This led to the concept of ischemic core and ischemic penumbra, respectively [6]. The penumbra represents salvageable tissue and is dynamic. If vessel occlusion persists, the penumbra may shrink due to progressive recruitment into the infarct core, a process enhanced by circumstances such as hypotension, acidosis, and fever. Alternatively it may return to a normal state following vessel recanalization or neuroprotective interventions.

Hyperthermia

A rise in body temperature after cerebral ischemia produces more extensive brain damage in rats and dogs [7, 8, 9]. Body temperatures higher than 37.5°C were recorded in 30% of acute ischemic stroke (AIS) patients during the first 24 hours of stroke onset and in 60% of patients when recorded for 72 hours [10].

Fever is associated with higher stroke mortality and poor outcome. In a prospective study of 260 patients with acute hemispheric stroke hyperthermia was independently related to higher stroke mortality, larger infarct volume and higher neurological deficit and dependency within the first 24 hours from stroke onset [10]. Mortality at 3 months was 1 % in normothermic patients compared with 16% in patients with fever. In another prospective study of 390 stroke patients a highly significant association between body temperature at admission and outcome was found [11]. Furthermore they found that for 1° C increase in body temperature the relative risk of poor

outcome rose by 2.2 and that 1°C rise in body temperature was equivalent to a 15 mm increase in infarct diameter. Whereas hyperthermia is clearly associated with poorer outcome in humans, it is yet unknown whether this association is causative or epiphenomenal.

Hypothermia in rodent models

Already in the 1950's a group of researchers found that occlusion of the middle cerebral artery in dogs resulted in smaller cerebral infarction when normal body temperature was lowered [12]. In rodent models of cerebral ischemia, hypothermia results in a significant increase in the number of surviving neurons as measured with histological examination after death [13-18]. In temporary brain ischemia models mild-to-moderate hypothermia is effective in infarct volume reduction and the earlier initiation of therapy offers the best clinical and radiologic benefit [19-21]. The permanent occlusion models show benefit when hypothermia is initiated within 1h [22, 23]. Recent studies that followed up animals for 2 months showed that hypothermia lasting 24 h is needed for sustained neuroprotection [24, 25]. Hypothermia after cerebral ischemia seems to diminish neurological defects [26, 27].

The evidence from animal models of ischemic stroke indicates that hypothermia affects a wide range of processes involved in ischemic brain damage, which suggests a great therapeutic potential for hypothermic therapy to alleviate the injuries after ischemic stroke.

Therapeutic hypothermia

Therapeutic effect has also been shown in clinical trials in various disorders. Recently two large randomized trials showed that lowering of body temperature to 32-34°C for 12- 24 h in comatose cardiac arrest patients significantly improved neurological outcome [28, 29]. Survival with good outcome was increased by 40 %. Two separate studies have also reported that therapeutic hypothermia improved the outcome of newborn infants with perinatal hypoxic- ischemic brain injury [30, 31].

The depth or duration of optimal hypothermia is not known. Moreover the rate of rewarming is not standardized. Mild-to-moderate hypothermia is generally defined as temperatures between 32°C and 35° C while severe hypothermia ranges between 28°C and 32°C. The majority of clinical trials studying brain protection after trauma, global anoxia or focal ischemia have selected moderate hypothermia. The duration of the hypothermic period ranges from 12 to 48 h in different studies [28, 32, 33]. Rates of rewarming vary depending on the study, but many authors advocate slow rewarming and a rate of 0.2°C/h.

Known adverse-effects of hypothermia

Hypothermia induces shivering, vasoconstriction and fluid losses thereby affecting electrolyte balances, prolongs bleeding time through its effects on platelets, and suppresses the immune system. These adverse effects can lead to adverse effects such as hypotension, cardiac arrhythmia and pneumonia which are commonly reported, especially in anesthetised patients with temperatures of 32- 33°C.

Therapeutic hypothermia in acute ischemic stroke

There is plenty of experimental evidence of therapeutic effect of hypothermia in AIS. A Cochrane review on cooling therapy for acute stroke found experimental evidence of a neuroprotective effect of hypothermia in AIS and trials with cooling therapy are needed.

Neuroprotectants have been studied as a method to potentially extend the time window to safely and effectively utilize reperfusion studies. The mechanism of neuroprotection by hypothermia is still

largely unknown. Hypothermia seems to counteract ischemic brain damage by several mechanisms: protection of the blood-brain-barrier (BBB), minimizing brain edema, reduction of intracranial hypertension, maintained mitochondrial function, and down regulating cerebral metabolism, for example suppressing release of excitatory amino acids [34-36].

Therapeutic hypothermia in the clinical setting in acute ischemic stroke

Therapeutic mild-to-moderate hypothermia has been tested in the clinical setting for two purposes: reduction of ischemic stroke volume as well as reduction of brain swelling and intracranial pressure after a large MCA territory infarction, where mild hypothermia is shown to be effective [37].

There are only six clinical studies in which patients with stroke received hypothermic therapy for neuroprotection, aiming to reduce the stroke volume. These studies are small feasibility and safety studies and heterogeneous in most of the variables that might determine the effect of cooling in stroke, such as the timing of the onset of hypothermia after stroke onset, target temperature, and the duration of cooling. Target temperature was 32-33°C in five studies [37- 41]. Such temperature reduction requires general anesthesia which brings the risk of complications. The possibility to monitor the clinical neurological status continuously is also lost with use of general anesthesia. Kammergaard and colleagues used the target temperature of 35.5°C, which allows cooling without anesthesia and may therefore reduce the risk of complications [42]. However the treatment may be less effective. The time from onset of stroke to initiation of cooling varied from 3 to 28 hours, and the time to required temperature from 3 to 11 hours. The duration of hypothermia varied from 6 h to several days. Five of the studies used surface cooling as a means to achieve target body temperature [37, 38, 40, 41, 42] , while COOLAD II Study utilised an endovascular device [39]. All of these studies concluded that hypothermia is safe and feasible in patients suffering from severe ischemic stroke.

No large randomized trials investigating the effect of hypothermia in patients with stroke have been completed. The Nordic Cooling Stroke Study (NOCSS) is an ongoing randomised controlled study designed to include 1000 patients and to assess efficacy of surface cooling system in awake acute stroke patients.

Medication needed during hypothermia treatment

It proved to be difficult to induce mild or moderate hypothermia in unanesthetized patients because thermoregulatory defences are well maintained in most stroke victims. Induction of therapeutic hypothermia is thus complicated by the need to overcome arteriovenous shunt vasoconstriction and shivering. Drugs known to markedly impair thermoregulatory defences are all anesthetics or major sedatives which produce respiratory depression.

Meperidine is an opioid with known antishivering properties. The downside to this drug is that larger doses may induce respiratory depression. The α_2 -agonists and 5-HT_{1A}- agonists are also an important class of antishivering drugs that produce little respiratory toxicity. Dexmedetomidine is an α_2 - agonist that blunts the central sympathetic system thereby providing analgesia without altering the respiratory drive significantly [44]. The combination of meperidine and dexmedetomidine in healthy subjects can reduce the shivering threshold without respiratory depression [44]. Buspirone is a 5-HT_{1A}-antagonist. When given alone, it can reduce the shivering threshold of healthy humans and is synergistic with meperidine in its antishivering properties [45]. The combination of medication allows for smaller doses of drugs thereby reducing the risk of respiratory depression. Magnesium sulfate has antishivering properties allowing it to speed the rate of cooling [46].

Hypothermia and thrombolysis

For a long time, researchers have tried to find ways of reducing the extent of the brain damage in AIS. Attempts to find pharmacological neuroprotectants have failed, despite huge economic investments. Thrombolysis reduces stroke volume but only a portion of patients seeks medical attention within the 3 h time window. Practically most AIS patients who present with significant neurological deficit within 3 h of symptom onset, and without an obvious contraindication will receive i.v- Actilyse- thrombolysis therapy. Recanalization of cerebral artery occlusion is seen in 50% of AIS patients who receive Actilyse- thrombolysis. By treating seven patients with Actilyse- thrombolysis we can prevent one patient from being in- hospitalized for the rest of his/her life.

Neuroprotectants have been studied as a method to potentially extend the time window to safely and effectively utilize reperfusion strategies. A plethora of experimental evidence suggests robust neuroprotection with hypothermia in AIS; studies in rodents have shown a reduction in infarct size, and that earlier initiation offers the best clinical and radiological results. Hypothermia is effective in temporary MCA models [19, 21], which aims to mimic the clinical scenario where the vessel is recanalized along with institution of hypothermia whereas the results in permanent MCA occlusion model are inconsistent. These studies emphasize the importance of designing trials aimed at utilizing neuroprotection in conjunction with recanalization therapies. In experimental studies there is evidence that hypothermia has no hazardous effect on thrombolysis- treatment [47].

A Phase I study entitled “Intravascular cooling in the treatment of stroke- longer tPA window” will address the question of whether hypothermia can extend the time window to administer tPA intravenously in AIS [101].

There are clinical safety and feasibility studies of mild hypothermia in AIS patients, but so far there are no controlled, randomized large studies whether hypothermia in AIS patients reduces the size of infarction and improves clinical outcome.

The risk of complication recorded in clinical studies using moderate hypothermia is most likely reduced with mild hypothermia as general anesthesia with its possible complications would be avoided. For the same reason it is likely to be feasible in stroke unit instead of intensive care unit which reduces the expenses of the treatment. Furthermore, the risk of complication is reduced by using a non- invasive Temperature Management System instead of an invasive endovascular cooling device. The possible neurological worsening can easily be detected in awake patients.

AIS is both disabling and lethal, many patients require chronic care and long- term institutionalization after stroke. The burden imposed upon health costs is tremendous. The risk of stroke increases with age and age adjusted rates of hospitalization for stroke is expected to rise, partly due to increase in life expectancy. With mild hypothermia treatment in acute stage of stroke we might improve the outcome of AIS- patients safely and decrease the burden to health costs of HUCH by decreasing the amount of long- term institutionalized patients.

Hypothesis:

Mild hypothermia with non- invasive cooling in awake patients is both safe and feasible.

STUDY DESIGN

Subjects and Methods

All patients presenting to the Emergency Department of Helsinki University Central Hospital with clinical signs and symptoms of AIS and treated with Actilyse- thrombolysis will be screened for the trial. If all inclusion criteria are met and no exclusion criteria are present, the patients will be approached to obtain written informed consent. The background of the proposed study and the benefits and risks of the procedures and study will be explained to the patient. The patient or legal representative must sign the consent form prior to enrollment.

Inclusion criteria:

- $18 \leq \text{Age} \leq 85$
- Hemispheric ischemic stroke
- Treated with Actilyse- (tPA) thrombolysis according to Meilahti protocol
- NIHSS 7-20 (after thrombolysis) or a significant paresis of the arm or the leg (NIHSS 3, no movement against gravity) or a significant dysfasia (NIHSS 2-3) despite of the total NIHSS score
- Symptom onset within 6 hour

Exclusion criteria:

- Platelet count $< 75,000/\text{mm}^3$
- Known coagulopathy (INR spontaneously >1.5)
- Hemodynamically unstable
- Recent history of angina pectoris or acute myocardial infarction (during the last year)
- Sepsis within 72 hours
- Pregnancy (females younger than 50 must undergo a pregnancy test)
- Patient with a clinically significant medical condition that, in the investigator's opinion, would make survival for the duration of the study unlikely, or would otherwise interfere with optimal participation in the study or produce a significant risk to the patient.
- Pre-existing neurological disability with modified Rankin Scale Score >2
- Known allergy or intolerance to buspirone, dexmedetomidine, meperidine, magnesium sulfate
- Intracranial hemorrhage in brain CT scan
- Intracranial mass lesion (i.e., abscess, tumor, or infection)
- Participation in an other therapy trial within last 3 months
- Hypothermia- treatment cannot be initiated within 6 hours of symptom onset
- Protocol violation in thrombolytic therapy
- Any condition where researchers assume that the patient is not suitable (must be reasoned)

Temperature Management System

The non-invasive Temperature Management System is a thermal regulating system composed of a control module and disposable, nonsterile Energy Transfer Pads. The system has been in commercial distribution since 2001.

The intended use of the device is to monitor and control patient temperature between 33-37°C. The control module pulls temperature-controlled water under negative pressure through the Energy Transfer Pads applied directly to the trunk and thighs. This results in heat exchange between the water and the patient.

Pre-randomization Procedures

- Medical history and physical examination
- Non-contrast head CT
- Pre-stroke mRS score
- NIHSS
- 12- lead ECG
- Chest X-ray
- TCD
- Screening laboratory tests: hemoglobin, platelet count, WBC, RBC, glucose, CK, CK-MBm, TnT, INR, APTT, krea, CRP, pregnancy test (women of childbearing potential), ALAT, GT

The results of all tests listed above must be reviewed prior to randomization to ensure that no exclusion criteria are present.

Randomization

Investigator will randomize patients via randomization envelopes. Patients will be randomized to either control (standard care) or active therapy (hypothermia) group.

All patients will be admitted to a specialized stroke unit after meeting randomization criteria where hypothermia will be immediately initiated in the experimental group of patients.

Procedures before treatment

- Insert nasogastric tube and initiate shivering protocol (only the patients randomized to hypothermia- treatment)
- Buspirone 20mg po/ nasogastric tube, then buspirone 20mg every 8th hour.
- Dexmedetomidine- infusion 2 ug/kg/h – 12 ug/kg/h.
- Meperidine 50mg i.v and supplemental doses of 25 mg i.v when needed
- A warming blanket/stockings placed over the chest, hands and feet.
- Insert urinary catheter with temperature probe
- Insert intra- arterial blood pressure monitor

Monitoring

- ECG (daily and continuous Holter- monitoring= ambulatory ECG recording)
- Arterial blood pressure (continuous intra- arterial monitoring)
- Oxygen saturation (continuous)
- Temperature- bladder (hourly)
- Near- infrared spectroscopy and EEG (continuous)
- laboratory tests:
 - TT, Hb, krea, CK, CK-mBm, TnT, INR, krea, CRP (daily)
 - Na, K, Cl, Mg, Ca-ion, Pi (twice a day)
 - glucose (four times a day)
 - pO₂, pCO₂, BE (as needed, at least four times a day)
 - EDTA- plasma and serum will be taken to later analysis for neuronal markers
- non- contrasted head- CT controlled within 24-48h from symptom onset
- Brain MRI within 7 days from symptom onset according to routine stroke protocol

Patient will be cooled to the core temperature of 35°C (urinary bladder temperature) with the non-invasive Temperature Management System used according to the instruction guide. Cooling will be started as soon as the patient has been transferred to stroke- unit (always within 6 hours of symptom onset). The initiation of hypothermia takes from 2 to 6 hours. Our aim is to initiate hypothermia within two hours after arriving to the emergency room and the treatment failure has been set at 36°C > 12 hours after symptom onset. The slow rewarming (0.2°C/hour) will be started after 12 hours of successful cooling, and normothermia in stroke patients would be 37°C. The systolic arterial pressure will be kept <220 and diastolic <120, and the mean arterial pressure >60.

Electrolytes will be kept within physiological ranges.

Normoglycemia will be maintained, and subcutaneous insulin will be administered according to Meilahti protocol.

ICP will not be measured but optimal head position will be provided and flexion and torsion will be avoided. Anti- edema treatment including hypertonic NaCl (3.5%) will be used to treat brain edema when necessary.

The patients will be intubated if needed, and will remain in the study.

Assessment of outcome

Brain CT will be repeated as soon as the patient reaches normothermia, no later than two days from the symptom onset. Brain MRI will be performed as soon as the patient co-operates sufficiently, preferably 7 days from symptom onset. Hemorrhagia and the size of infarction will be assessed by the brain MRI. All MR measurements will be done at 1.5 Tesla on a Siemens Scanner. The MRI protocol will include scout images, DWI, T1, T2, FLAIR, T2*, and MR angiography. This protocol can be completed in 30-40 minutes. Hemorrhagia will be graded according to SITS scale:

- ☐ HI 1: small petechiae along the margins of the infarct
- ☐ HI 2: a more confluent petechiae within the infarct area but without space-occupying effect
- ☐ PH 1: blood clot(s) not exceeding 30% of the infarct area with some mild space-occupying effect
- ☐ PH 2: blood clots exceeding 30% of the infarct area with significant space occupying effect

Neuropsychological tests will be performed slightly before the 3 month clinical visit. GOS, mRS, Barthel and NIHSS will be tested at the 3 months and 12 months visit.

Timetable and members of the research group:

Recruitment of patients begins in January 2007. We assume to recruit 36 patients by the end of 2008.

Patients will be recruited by Dr. Katja Piironen and Dr. Janne Leinonen. This study is a PhD project of Dr. Katja Piironen and the projected working time for the recruitment of patients is 50% of the weekly working hours for Dr. Katja Piironen and 20% for Dr. Janne Leinonen during 2007- 2008. NIRS and EEG recordings will be initiated by TkL Tommi Noponen and DI Kalle Kotilahti, and projected working time is 25% of the weekly working hours for each. Dr. Ville Pettilä will take care of the sedation of the patient in hypothermia initiation and projected working time is 10% of weekly working hours. For the other members of the group it will be 20% for Dr. Turgut Tatlisumak and Dr. Marjaana Tiainen, 10% for Dr. Jyrki Mäkelä, 5 % for Dr. Risto Roine and Dr. Oili Salonen and 25% for DI Lauri Lipiäinen, Ms. Tiina Näsi and Mr. Jaakko Virtanen.

Safety and ethical considerations:

Non- contrast brain CT, brain MRI, chest X- ray, continuous EEG, continuous ECG and continuous intra- arterial blood pressure monitoring will be performed according to routine clinical practice. TCD is a non- invasive and safe method and is routinely used in stroke patients (katso liite "Transkranieelli Doppler"). NIRS is a relatively new medical imaging method. It is completely non- invasive, does not utilize magnetic fields or expose tissue to ionising radiation. It has been successfully used in healthy volunteers and patients of intensive care unit (katso liitteet "Near-infrared spectroscopy", "Tutkimuksessa käytettävät EEG- ja NIRS- laitteet"). The NIRS and EEG equipment is provided by GE Healthcare Finland (katso liite "Teknillinen korkeakoulu ja GE Healthcare Finland").

This study and the methods used are ethically appropriate as aiming at developing a novel therapy for AIS patients and similar approaches have already been implanted in other patient populations (resuscitated patients).

We expect improved outcome of AIS patients treated with Actilyse- thrombolysis and mild hypothermia. Outcome would be defined by improvement in clinical test batteries and reduction of the infarction size. In case of favourable results, we will design a multicenter efficacy trial.

Expected results:

We expect mild hypothermia to be safe and feasible in awake AIS patients treated in a stroke unit.

REFERENCES:

1. Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. *Stroke*. 2000 Jul;31(7):1588-601.
2. American Heart Association. Stroke. In: Heart Disease and Stroke Statistics- 2003 Update. American Heart Association, TX, USA (2003).
3. The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group. Tissue Plasminogen activator for acute ischemic stroke. *N. Engl. J. Med.* 333(24), 1581- 1587 (1995).
4. Christou I, Felberg RA, Demchuck AM et al. Intravenous tissue plasminogen activator and flow improvement in acute ischemic stroke patients with internal carotid artery occlusion. *J Neuroimaging*. 2002 Apr;12(2):119-23.
5. Demchuck AM, Burgin WS, Christou I et al. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke*. 2001 Jan;32(1):89-93.
6. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. *Stroke*. 1981 Nov-Dec;12(6):723-5.
7. Kim Y, Busto R, Dietrich WD, Kraydieh S, Ginsberg MD. Delayed postischemic hyperthermia in awake rats worsens the histopathological outcome of transient focal cerebral ischemia. *Stroke*. 1996 Dec;27(12):2274-80; discussion 2281.
8. Baena RC, Busto R, Dietrich WD, Globus MY, Ginsberg MD. Hyperthermia delayed by 24 hours aggravates neuronal damage in rat hippocampus following global ischemia. *Neurology*. 1997 Mar;48(3):768-73.
9. Wass CT, Lanier WL, Hofer RE, Scheithauer BW, Andrews AG. Temperature changes of ≥ 1 degree C alter functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia. *Anesthesiology*. 1995 Aug;83(2):325-35.
10. Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. *Stroke*. 1998 Dec;29(12):2455-60.
11. Reith J, Jorgensen HS, Pedersen PM. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996 Feb 17;347(8999):422-5.
12. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. *Am J Physiol*. 1954 Oct;179(1):85-8.
13. Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab*. 1987 Dec;7(6):729-38.
14. Barone FC, Feuerstein GZ, White RF. Brain cooling during transient focal ischemia provides complete neuroprotection. *Neurosci Biobehav Rev*. 1997 Jan;21(1):31-44. Review.
15. Onesti ST, Baker CJ, Sun PP, Solomon RA. Transient hypothermia reduces focal ischemic brain injury in the rat. *Neurosurgery*. 1991 Sep;29(3):369-73.
16. Ooboshi H, Ibayashi S, Takano K. Hypothermia inhibits ischemia-induced efflux of amino acids and neuronal damage in the hippocampus of aged rats. *Brain Res*. 2000 Nov 24;884(1-2):23-30.
17. Yamashita K, Eguchi Y, Kajiwarra K, Ito H. Mild hypothermia ameliorates ubiquitin synthesis and prevents delayed neuronal death in the gerbil hippocampus. *Stroke*. 1991 Dec;22(12):1574-81.
18. Zhang Y, Wong KC, Zhang Z. The effect of intraischemic mild hypothermia on focal cerebral ischemia/reperfusion injury. *Acta Anaesthesiol Sin*. 2001 Jun;39(2):65-9.
19. Huh PW, Belayev L, Zhao W, Koch S, Busto R, Ginsberg MD. Comparative neuroprotective efficacy of prolonged moderate intraischemic and postischemic hypothermia in focal cerebral ischemia. *J Neurosurg*. 2000 Jan;92(1):91-9.

20. Kollmar R, Schabitz WR, Heiland S. Neuroprotective effect of delayed moderate hypothermia after focal cerebral ischemia: an MRI study. *Stroke*. 2002 Jul;33(7):1899-904.
21. Colbourne F, Corbett D, Zhao Z, Yang J, Buchan AM. Prolonged but delayed postischemic hypothermia: a long-term outcome study in the rat middle cerebral artery occlusion model. *J Cereb Blood Flow Metab*. 2000 Dec;20(12):1702-8.
22. Doefler A, Schwab S, Hoffmann T, Engelhorn T, Forsting M. Combination of decompressive craniectomy and mild hypothermia ameliorates infarction volume after permanent focal ischemia in rats. *Stroke*. 2001 Nov;32(11):2675-81.
23. Baker CJ, Onesti ST, Solomon RA. Reduction by delayed hypothermia of cerebral infarction following middle cerebral artery occlusion in the rat: a time-course study. *J Neurosurg*. 1992 Sep;77(3):438-44.
24. Colbourne F, Corbett D, Zhao Z, Yang J, Buchan AM. Prolonged but delayed postischemic hypothermia: a long-term outcome study in the rat middle cerebral artery occlusion model. *J Cereb Blood Flow Metab*. 2000 Dec;20(12):1702-8.
25. Corbett D, Hamilton M, Colbourne F. Persistent neuroprotection with prolonged postischemic hypothermia in adult rats subjected to transient middle cerebral artery occlusion. *Exp Neurol*. 2000 May;163(1):200-6.
26. Colbourne F, Corbett D. Delayed postischemic hypothermia: a six month survival study using behavioral and histological assessments of neuroprotection. *J Neurosci*. 1995 Nov;15(11):7250-60.
27. Kwon JY, Bacher A, Deyo DJ. Effects of hypothermia and lamotrigine on trace-conditioned learning after global cerebral ischemia in rabbits. *Exp Neurol*. 1999 Sep;159(1):105-13.
28. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 346(8), 549- 556 (2002).
29. Bernard SA, Gray TW, Buist MD. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002 Feb 21;346(8):557-63.
30. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Polin RA, Robertson CM, Thoresen M, Whitelaw A, Gunn AJ. et co: Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet*. 2005 Feb 19-25;365(9460):663-70
31. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH; National Institute of Child Health and Human Development Neonatal Research Network. Whole body hypothermia for neonates with hypoxic- ischemic encephalopathy. *N Engl J Med*. 2005 Oct 13;353(15):1574-84.
32. Bernard SA, Gray TW, Buist MD. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002 Feb 21;346(8):557-63.
33. Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR Jr, Muizelaar JP, Marion DW, Luerksen TG. Hypothermia on admission in patients with severe brain injury. *J Neurotrauma*. 2002 Mar;19(3):293-301.
34. Dietrich WD, Busto R, Halley M, Valdes I. The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia. *J Neuropathol Exp Neurol*. 1990 Sep;49(5):486-97.
35. Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke*. 1989 Jul;20(7):904-10.
36. Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *J Neurosurg*. 1993 Sep;79(3):363-8.

37. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke*. 1998 Dec;29(12):2461-6.
38. Naritomi H, Shimizu T, Oe H, Kinugawa H, Sawada T, Hirata T. Mild hypothermia is effective for the treatment of acute embolic stroke if induced in 24 hours after onset but not in the later phase. *J Stroke Cerebrovasc Dis* 1996; 6 (suppl 4): 75
39. Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. *Stroke*. 2001 Nov;32(11):2550-3.
40. Krieger DW, De Georgia MA, Abou- Chebl A et al. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. *Stroke*. 2001 Aug;32(8):1847-54.
41. Schwab S, Georgiadis D, Berrouscot J, Schellinger PD, Graffagiano C, Mayer S. Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke*. 2001 Sep;32(9):2033-5.
42. Kammersgaard LP, Rasmussen BH, Jorgensen HS, Reith J, Weber U, Olsen T. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling. *Stroke*. 2000 Sep;31(9):2251-6. *ling: A case-control study: the Copenhagen Stroke Study*.
43. Venn RM, Hell J, Grounds RM.. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care*. 2000;4(5):302-8. Epub 2000 Jul 31.
44. Doufas AG, Lin CM, Suleman MI. Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. *Stroke*. 2003 May;34(5):1218-23. Epub 2003 Apr 10.
45. Mokhtarani M, Mahgoub AN, Morioka N. Buspirone and meperidine synergistically reduce the shivering threshold. *Anesth Analg*. 2001 Nov;93(5):1233-9.
46. Zweifler RM, Voorhees ME, Mahmood A, Parnell M Magnesium sulfate increases the rate of hypothermia via surface cooling and improves comfort. *Stroke*. 2004 Oct;35(10):2331-4. Epub 2004 Aug 19.
47. Kollmar R, Henninger N, Bardutzky J, Schellinger PD, Schabitz WR, Schwab S. Combination therapy of moderate hypothermia and thrombolysis in experimental thromboembolic stroke-an MRI study. *Exp Neurol*. 2004 Nov;190(1):204-12.

Websites:

101. Intravascular cooling in the treatment of Stroke- Longer tPA window.
www.innercool.com/news/pr_20030630.htm