Cooling therapy for acute stroke (Review)

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ABSTRACT

Background
Recent studies in acute stroke patients have shown an association between body temperature and prognosis.

Objectives
Our objective was to assess the effects of cooling when applied to patients with acute ischaemic stroke or primary intracerebral haemorrhage.

Search strategy
We searched the Cochrane Stroke Group's trial register (last searched in March 1999), plus MEDLINE searched up to November 1998 and EMBASE searched from January 1980 to November 1998. We contacted investigators, pharmaceutical companies and manufacturers of cooling equipment in this field.

Selection criteria
All completed randomised controlled trials or controlled clinical trials, published or unpublished, where cooling therapy (therapy given by physical devices or antipyretic drugs primarily to lower body temperature independently of basal temperature at the beginning of treatment) was applied up to two weeks of an acute ischaemic stroke or primary intracerebral haemorrhage.

Data collection and analysis
Two reviewers independently searched for relevant trials.

Main results
No randomised trials or controlled trials were identified; one placebo-controlled trial of metamizol is currently underway.

Authors' conclusions
There is currently no evidence from randomised trials to support the routine use of physical or chemical cooling therapy in acute stroke. Since experimental studies showed a neuroprotective effect of hypothermia in cerebral ischaemia, and hypothermia appears to improve the outcome in patients with severe closed head injury, trials with cooling therapy in acute stroke are warranted.

PLAIN LANGUAGE SUMMARY

No evidence to support the use of cooling therapy within the first two weeks after a stroke

Stroke is the third most common cause of death and a leading cause of long-term disability worldwide. Extreme cooling of the body temperature (hypothermia) may possibly protect the nervous system from damage during stroke and some evidence has suggested that people with a lower body temperature at the time of a stroke do better later than those with a higher temperature. Cooling is used in neurosurgery, open-heart surgery, and severe closed-head injury to protect patients. The authors of this Cochrane review looked for evidence that cooling the body would benefit patients during or in the two weeks after a stroke. They looked for studies on the use of physical or chemical cooling therapy on patients within two weeks of having a stroke. Physical cooling techniques would include

cooling blankets, use of ice, fans, or other devices. Chemical cooling techniques would include drugs used to reduce fever, like aspirin or acetaminophen. The authors looked for studies on two types of stroke patients: those with acute ischaemic stroke (when a blood clot blocks blood flow to the brain), and those with primary intracerebral haemorrhage (when a blood vessel in the brain ruptures). The review authors did not find any randomized controlled trials or controlled clinical trials on cooling therapy for stroke. These types of studies are the best type of evidence for whether a therapy works, because they limit the errors that may be introduced into a study. The authors did find a major trial in progress, using the drug metamizol for cooling. The review authors could not recommend the use of cooling therapy for stroke patients since there was no completed research that showed this therapy to be effective and safe.

BACKGROUND

Stroke is the third commonest cause of death after coronary artery disease and all cancers, not only in developed countries but world wide (Murray 1997) and one of the leading causes of long-term disability.

Despite their effectiveness in animal models of stroke, clinical trials of neuroprotective agents in humans have provided disappointing results (Ad Hoc Consensus1998) and so, other means of neuroprotection should be sought. There are references from decades ago that show in animals that hypothermia confers protection against the neuronal injury produced by episodes of transient cerebral ischaemia (Mellergard 1992). The mechanisms are not fully understood. Hypothermia is known to decrease the cerebral metabolic rate, and there is good evidence that at least some of the neuroprotection of hypothermia is due to the associated decrease of metabolic demand (Michenfelder 1988). Recent studies have shown that while hypothermia (33 degrees Celsius) does not preserve high-energy phosphate (e.g. ATP. phosphocreatinine) or prevent accumulation of metabolic waste (e.g. lactate) (Busto 1989), it does confer histopathologic protection from ischaemia (Busto 1987). Considerable evidence has now accumulated from neuronal cultures and in vivo animal experiments that excitotoxic amino acids (particularly glutamate and aspartate) play an important role in the evolution of ischaemic brain damage (Benveniste 1989, Choi 1988). Moderate hypothermia is associated with a decrease in the extracellular levels of glutamate during ischaemia in rats (Busto 1989) and glycine in rabbits (Baker 1991) and the beneficial effects of hypothermia is mediate, at least in part, by the attenuation of release of excitatory amino acids.

Profound hypothermia is already applied in neurosurgery and open-heart surgery to counter the effects of cerebral hypoxia (Chyatte 1989, Saccani 1992) and in severe closed head injury moderate (33 - 32 degrees Celsius) hypothermia appears to improve outcome (Marion 1993, Marion 1997, Signorini 1999). Although recent studies in acute stroke patients have shown an association between body temperature and prognosis (Reith 1996, Azzimondi 1995, Castillo 1994) insufficient information is currently available in humans to explain and quantify any protective effect of hypothermia and the detrimental effect of hyperthermia on neurological damage after global or focal cerebral ischaemia. Also some temperature lowering agents, like non steroidal anti-inflammatory drugs, have antiplatelet activity and could increase the risk of bleeding in acute ischaemic and haemorrhagic stroke (IST 1997, CAST 1997). Other risks associated with induced hypothermia are mainly, sepsis, pneumonia and coagulopathy (Schubert 1995).

This systematic review aims to assess the relationship between imposed changes in body temperature and outcome after acute stroke and determine whether there is any clear evidence that cooling therapy of any kind is beneficial, or whether the intervention is sufficiently promising to merit further trials.

OBJECTIVES

To determine whether cooling (with antipyretic drugs or with physical devices) is safe and effective when applied to patients with acute ischaemic stroke and primary intracerebral haemorrhage.
We wished to test the hypotheses.
(1) That cooling therapy reduces the risk of a "poor-outcome" (ie being dead or dependent on others in activities of daily living) several months after stroke.
(2) That cooling therapy increases the risk of intracranial haemorrhage (in patients with ischaemic stroke), rebleeding in patients with primary intracerebral haemorrhage, and extracranial bleeding.
(3) That cooling therapy increases the risk of pneumonia and coagulopathy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCT) and controlled clinical trials (CCT) of cooling versus control (placebo or open control) were considered eligible.

Types of participants

Patients of any age or sex treated up to two weeks after an acute ischaemic stroke (CT scan or MRI demonstrates an infarction or is normal) or primary intracerebral haemorrhage (CT scan or MRI demonstrates intracerebral haemorrhage).

Types of intervention

Cooling therapy (therapy given by physical devices or antipyretic drugs primarily to lower body temperature independently of basal temperature at the beginning of treatment).
(a) Physical cooling: fluid-filled cooling blanket, ice-water lavage, 'bear-hugger' air-cooling device, cold infusions or any combination of above, or other methods.
(b) Chemical cooling (antipyretic drugs) - non steroidal anti-inflammatory drugs (aspirin more than 500 mg three times a day or equivalent doses of other anti-inflammatory drugs (Cyclo-oxygenase inhibitors), paracetamol and acetominophen - by any route.

Types of outcome measures

(1) Poor outcome at the end of follow-up. This is defined as death or dependency, as measured by the Rankin or Barthel scales, or another method by which it is clear how many people are dependent and how many are independent. Many would regard this as the most important outcome since the aim of treatment should be not only to prevent death but to prevent serious disability in survivors.
(2) Death from all causes (i) within one month, and (ii) during the whole follow-up period.
(3) Intracranial haemorrhage (both symptomatic and asymptomatic) demonstrated by CT or MR scan, or autopsy
(4) Extracranial haemorrhage.
(5) Frequency of other complications such as pneumonia, coagulopathy, or other serious adverse events during treatment and follow-up period.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Stroke Group methods used in reviews.

This review has drawn on the search strategy developed for the Stroke Group as a whole. All possibly relevant trials were identified in the Specialised Register of Controlled Trials (see Review Group Details for more information). The Register was last searched by the Review Group Coordinator for this review in March 1999 using a search strategy designed to identify all relevant trials. Additional searches of Medline and EMBASE were made to supplement the Stroke Group general strategy. Stroke-specific terms from the search strategy were combined with the following controlled vocabulary and free text terms:

MEDLINE (Ovid). Years searched 1966-November 1998
MeSH Terms: Exp BODY TEMPERATURE; TEMPERATURE; COLD; HYPOTHERMIA; HYPOTHERMIA, INDUCED; FEVER; CRYOTHERAPY
Text words: Hypothermia; cold$; cool$; temperature$

EMBASE (Ovid). Years searched 1980-November 1998
ENTREE Headings: Exp TEMPERATURE; LOW TEMPERATURE PROCEDURES; CRYOTHERAPY; INDUCED HYPOTHERMIA; PROFOUND INDUCED HYPOTHERMIA; HYPOTHERMIA.
Text words: Hypothermia; cold$; cool$; temperature$.

Additionally citations in the reference lists from publications identified as mentioned above were checked.

Unpublished (or published) work on cooling therapy in acute stroke was checked in personal contacts with investigators interested in stroke during meetings.

We contacted the following pharmaceutical companies to identify further published, unpublished or ongoing studies: Bayer (Aspirin), Smithkline Beecham (Paracetamol, Nabumetone), Parke-Daves (Meclofenamate sodium), Upsamedica (Niflumic acid), Diamant (Tiaprofenic acid), Sigma (Tolfenamic acid), Medibial (Acemetacine), Jansen-Cilag (Naproxen), Searle / Geig (Diclofenac), Wyeth (Etodolac. Fentiazac), Bial (Etofenamato), Basi (Fenbufen), Helsinn (Fentiazac, Nimesulid), Knoll (Flurbiprofen, Ibuprofen), Upjohn (Ibuprofen), Merck, Sharp & Dohm (Indomethacin, Sulindac), Alter (ketoprofen), Byk (Lonazolac), Pfizer (Piroxicam), Roche (Tenoxicam), Delta (Proglumetacina) - and Manufacturers of cooling equipment - Cincinnati Sub-Zero Products, Inc., Helsinn Healthcare).

METHODS OF THE REVIEW

Two of us (MC, MV) independently searched for RCTs and CCTs for inclusion in the review but found none. If any are found in the future we plan that: disagreement will be resolved by discussion, the same two reviewers will assess the methodological quality of each trial, no scoring system will be used to assess the quality of each but details of randomisation method, including whether intention-to-treat analysis were possible from the published data, the number of patients lost to follow-up and if there was a blinded outcome assessment will be checked; data will be independently extracted by the same two reviewers and cross-checked; any discrepancies will be discussed and decisions documented; from the papers we will collect data on: age; gender; stroke type and delay since stroke; type dosing procedure and route of antipyretic drug, physical cooling method, lowest body temperature attained, time between initial symptoms and cooling, the duration that cooling was applied, neurological deterioration, mortality and morbidity details. For RCTs and quasi-randomised trials we will test for heterogeneity and calculate a weighted estimate of the typical treatment effect across trials (odds ratio). We will also perform sensitivity analysis, as appropriate, comparing firstly truly randomised and quasi-randomised trials, and secondly placebo and open controlled trials. Analysis will be made for all strokes and independently for ischaemic and haemorrhagic strokes. Analysis also will be made for all types of cooling therapy and independently for physical cooling and chemical cooling for the following ranges of body temperature: more or equal to 37 degrees Celsius; more or

equal to 36 degrees Celsius and less than 37 degrees Celsius; more or equal to 35 degrees Celsius and less than 36 degrees Celsius; less than 35 degrees Celsius. All analyses will be based on "intention-to-treat" principle where possible. If the published information doesn't allow an intention-to-treat analysis we will contact the authors to get as complete follow-up as possible on all randomised patients for the originally proposed period of follow-up. If the Rankin scale or Barthel scale scores are not available we will define poor-outcome based on the clinical information. A poor outcome will be considered if the patient requires a high level of supported care.

This review was prepared using the Cochrane software package RevMan version 3.1.

DESCRIPTION OF STUDIES

No completed trials of physical or chemical cooling therapy in acute ischaemic stroke or primary intracerebral haemorrhage were identified. Fifteen trials of aspirin in acute stroke were identified, but none used an antipyretic dose. These trials were reviewed by two of us (MC, MV). No completed trials with other non steroidal anti-inflammatory drugs in acute stroke were identified. One of us (MC) reviewed 1864 titles and abstracts as a result of MEDLINE search and 1701 titles and abstracts as a result of EMBASE search. A randomised placebo controlled clinical trial of metamizol (2000 mg three times a day, intravenous) is currently underway and should be finished by the end of 1999 (ATIS 1998). Metamizol is a Pyrazolon derivative and considered in the group of the non steroidal anti-inflammatory drugs with antipyretic, analgesic and anti-inflammatory properties. A feasibility and safety study on physical cooling for a period of six hours by the "forced air " method in acute stroke showed that modest hypothermic therapy (body temperature 35.5 - 36 degrees Celsius) does not seems to be harmful, as it is not associated with increased frequency of complications or increased mortality (Kammersgaard 1999). Also moderate (33 degrees Celsius) hypothermia by cooling blankets and cool ventilator air fanning methods, prolonged for 48 - 72 hours is not associated with severe side effects (Schwab 1998).

METHODOLOGICAL QUALITY

Not applicable

RESULTS

Not applicable

DISCUSSION

We did not identify any completed randomised trials of physical or chemical cooling methods in acute stroke. Although there have been trials of aspirin, none used an antipyretic dose. A trial of a chemical cooling agent (ATIS 1998) is underway. Physical cooling methods appear feasible in acute stroke (Kammersgaard 1999) and in head injury (Signorini 1999), so a randomised controlled trial in acute stroke is justified.

AUTHORS' CONCLUSIONS

Implications for practice

There are no completed randomised controlled trials of physical or chemical cooling in acute ischaemic stroke or primary intracerebral haemorrhage. Routine application of such therapy cannot be recommended at present.

Implications for research

Experimental studies show that hypothermia confers protection against the neuronal injury produced by cerebral ischaemia. In humans hypothermia is already applied in neurosurgery and open-heart surgery. Also in severe closed head injury hypothermia seems to hasten neurological recovery and the outcome. Hence, trials with physical or chemical cooling, as a neuroprotection, in humans with acute stroke are needed.

POTENTIAL CONFLICT OF INTEREST

None

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External sources of support

- No sources of support supplied

Internal sources of support

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ATIS - Antitermic Ischemic Stroke. Unpublished.

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TABLES

Characteristics of ongoing studies

Study	ATIS 1998
Trial name or title	Antitermic Ischemic Stroke
Participants	Acute ischaemic stroke until 48 hours after initial symptoms and body temperature between 37 degrees C and 38 degrees C. Size: 250 patients
Interventions	Metamizol (2000mg three times a day, intravenous) vs placebo. Metamizol is a pyrazolon derivative and considered in the group of the non steroidal anti-inflammatory drugs with antipyretic, analgesic and anti-inflammatory properties
Outcomes	Score on Scandinavian Stroke Scale at 7, 30 and 90 days after stroke and infarction volume at 90 days
Starting date	October 1998
Contact information	Dr Jose Castillo, Dept of Neurology, Hospital Xeral de Galicia, 15705 Santiago de Compostela, Spain. Fax: 34 81 570102; email: mecasti@usc.es
Notes	

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hypothermia, Induced; Stroke [*therapy]

MeSH check words

Humans

COVER SHEET

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Authors	Correia M, Silva M, Veloso M
Contribution of author(s)	Dr Manuel Correia: Conception and design of the review; development of all stages of the review; drafting the review and revising the review according to comments; final version to be published. Dr Miguel Veloso: Undertaking searches; assessing the trials for inclusion criteria and extracting data if appropriate; contact with pharmaceutical companies. Dr Mário Silva: Contact wit pharmaceutical companies.
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