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Cooling therapy for acute stroke (Protocol)

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Cooling therapy for acute stroke

Abid Malik¹, Rachna Begh², Saleema Roze³, Kelda Green³, Nicola Lindson²

¹Hyper Acute Stroke Unit, Charing Cross Hospital, London, UK. ²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. ³University of Liverpool, Liverpool, UK

Contact address: Abid Malik, Hyper Acute Stroke Unit, Charing Cross Hospital, Fulham Palace Road, Hammersmith, London, W6 8RF, UK. abidmalik@nhs.net.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of temperature cooling compared to standard stroke care in people with acute stroke.

BACKGROUND

Description of the condition

A stroke occurs due to an interruption of blood supply to the brain. The lack of blood supply leads to the rapid loss of neuronal tissue and the development of a neurological deficit. The interruption of blood supply is most commonly due to a blood vessel becoming blocked by a blood clot or by the rupture of a blood vessel and the subsequent intracranial haemorrhage (www.stroke.org.uk).

Strokes account for the second-largest cause of mortality and the largest cause of complex disability worldwide. Approximately 6.2 million deaths worldwide are due to direct effects following a stroke and the number of people affected is set to double in the next 15 years ([Feigin 2013](#); [Stroke Association 2018](#)). A stroke often leaves physical and psychological morbidity. There is also significant associated emotional and carer stress. Sixty-nine per cent of stroke survivors are unable to return to work and one in five is cared for by friends and family ([Stroke Association 2016](#)).

Hyperthermia, a temperature of more than 37.5 °C, is a common occurrence in acute stroke, occurring in 40% to 61% of patients

in the first seven days following the attack. Those with a high temperature have a higher mortality than those who are normothermic ([Wrotek 2011](#)). Hyperthermia has been shown in experimental studies to be associated with a larger infarct volume and poorer outcomes in terms of mortality and morbidity ([Hajat 2000](#); [Kim 1996](#); [Krieger 2001](#)). The relationship between high body temperature and stroke outcome was explored in a meta-analysis of nine studies that included 3790 participants. A significant increase in morbidity and mortality was identified in patients with a raised body temperature and research into the effects of temperature-lowering therapy was suggested ([Hajat 2000](#)).

The physiological mechanisms for poorer neurological outcomes in hyperthermic conditions are not well understood. Animal models of acute cerebral ischaemia have shown hyperthermia potentiates an increase in the permeability of the blood-brain barrier, free radical formation, and metabolic demands. The change in cellular mechanisms lead to larger infarct sizes and a poorer outcome ([Den Hertog 2009a](#)).

Description of the intervention

Induced hypothermia and cooling to normothermia are neuroprotective interventions. The use of hypothermia has been well recognised in preventing cerebral ischaemia during cardiac surgery. By inducing hypothermia during cardiopulmonary bypass, safe cardiac surgery can be performed whilst reducing the blood supply to the brain without the risk of cerebral hypoxic injury (Sunde 2011). Similarly, hypothermia is now the standard practice in postcardiac arrest-related coma and has been shown to reduce fatality and improve neurodevelopment in neonates with hypoxic brain injury (Andresen 2015).

How the intervention might work

Targeting hyperthermia in acute stroke, either by cooling to normothermic levels (temperature of 36.5 °C to 37.5 °C) or hypothermic levels (temperature of less than 36 °C) has been proposed as a potential method of improving mortality and functional outcomes. Body temperature can be cooled, often to normothermic levels, using pharmacological methods, such as paracetamol or ibuprofen. Alternatively, physical methods exist, such as the application of cooling pads, infusing cooled liquids, or by inserting a cooling catheter into the central venous circulation.

Why it is important to do this review

Treatments for acute stroke are limited. The use of aspirin in the first 48 hours, intravenous thrombolysis, nursing in a stroke unit, and mechanical thrombectomy are the only recommended, efficacious treatments for an ischaemic stroke (Motyer 2017; Wardlaw 2009). However, the use of mechanical thrombectomy requires significant investment in infrastructure and training, and the availability of these treatments are limited worldwide, especially in low- to middle-income countries (Ganesh 2018; Jayaraman 2017; Murray 2015; NICE guideline 2008).

Strokes due to intracerebral haemorrhage fare worse, with limited acute treatment options, such as stabilisation of physiological parameters, reversal of clotting derangement, and access to neurosurgical interventions in the situation of raised intracranial pressure (Morgenstern 2010). Despite these treatments, mortality and morbidity remain high, with less than half of patients surviving one year, and less than one-third surviving five years (Poon 2014). The need for an effective and accessible treatment for stroke was reflected in the UK Government's National Stroke Strategy for England, which prioritised research and development in stroke medicine (Department of Health 2007). Cooling to normothermic levels or inducing hypothermia is a promising tool to either treat, or extend the time window for alternative treatments, in the case of an acute stroke.

Previous Cochrane Review and meta-analysis: the rationale for an update

This review will update a Cochrane meta-analysis conducted by Den Hertog et al (Den Hertog 2009b). There have been several developments since previous publication of the review that necessitate an update. First, the meta-analysis was conducted at a time when the only available physical temperature reduction trials were small and of low quality (Den Hertog 2009b). As a result, the review authors chose to include two trials that were not randomised, as they were pilot studies conducted to test feasibility (Kammersgaard 2000; Krieger 2001). These studies used consecutive enrolment and those not eligible were allocated as controls. Therefore, the two studies were at a high risk of selection bias. For this update, we have chosen to only include randomised controlled trials (RCTs) to reduce the risk of bias and, therefore, we will exclude Krieger 2001 and Kammersgaard 2000.

Second, previous iterations of the review did not specify any criteria for eligible study control groups. To be eligible for inclusion in the update of this review the intervention must be compared to 'standard stroke care' - equal access to thrombolysis (intravenous or intra-arterial), thrombectomy, antiplatelet agents, and treatment in a specialist stroke unit - as all of these factors have been found to have an effect on relevant outcomes. This will mean that two previously included studies will no longer be eligible. Kammersgaard 2000 will be ineligible as it is a non-randomised trial. We have also excluded the study NCT02184260, which was previously included in the Cochrane Review, as this study used the antipyretic, metamizole, for pharmacological cooling. Metamizole has subsequently been withdrawn due to a severe side effect profile, including agranulocytosis. Therefore, the applicability of this study is now in question as the side effect profile may have influenced the risk of infections.

The results of the previous review were inconclusive and exposed the need for further research with better quality studies (Den Hertog 2009b). It also identified three studies that were ongoing at the time of publication (De Ridder 2017; Den Hertog 2009a; Lyden 2016). The results of these studies have now been published. These studies comprise the largest- and highest-quality pharmacological and physical temperature reduction trials to date, necessitating an up-to-date meta-analysis.

Finally, the previous version of the review did not use a standardised tool for assessing the risk of bias in the included studies. Allocation concealment, blinding, and randomisation were reported upon in the 'Characteristics of included studies' section and incomplete data and selective reporting were discussed in the review text, but no synthesis or graphical representation was available. We will perform a comprehensive 'Risk of bias' assessment using Cochrane's 'Risk of bias' tool, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

OBJECTIVES

To assess the efficacy and safety of temperature cooling compared to standard stroke care in people with acute stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with a parallel design that involve participants randomised to cooling versus standard stroke care.

Types of participants

We will include adults who have experienced intracerebral bleeding or ischaemic strokes, confirmed by computed tomography (CT) scanning or magnetic resonance imaging (MRI). As we are dealing with acute strokes, participants must present and start treatment within 24 hours of onset of stroke symptoms. Where this information is not given clearly in a paper, we will contact study authors. We will exclude trials that have included participants presenting with stroke signs after 24 hours.

Types of interventions

We will include studies that provide intervention participants with temperature-lowering therapy (cooling) for a minimum of 12 hours. Temperature-lowering management is defined as either maintenance of normothermia (temperature of 36.5 °C to 37.5 °C) or induction of therapeutic hypothermia. We define therapeutic hypothermia or targeted temperature management - according to standardised criteria - as maintaining a core body temperature of less than 36 °C for a minimum of 12 hours (Sunde 2011). In this review we are looking specifically at temperature-lowering therapies in the acute stroke patient regardless of the initial body temperature. The aim of the review is not to investigate treatment of fever, as we are taking a broader overview of temperature-lowering in stroke, and will include all patients regardless of initial body temperature.

At time of publication, methods of temperature-lowering therapy include physical methods of cooling, such as the application of cooling pads, infusion of cooled liquids, or insertion of a cooling catheter into the central venous circulation, or pharmacological temperature reduction methods, such as the administration of paracetamol (acetaminophen), ibuprofen, or a combination of medications.

In order to be included, studies that aimed to induce hypothermia must also have used a verified, digital method of core temperature recording. Methods include the use of a bladder probe, rectal thermometer, or endovascular temperature monitoring. The use of a digital method of core body temperature monitoring reduces measurement errors and ensures close monitoring of intracorporeal temperature. Invasive temperature monitoring is not needed in pharmacological temperature reduction studies, as only small changes in temperature levels are expected, and invasive monitoring would be deemed unacceptable.

Comparators

We will include studies that compared cooling therapies plus 'standard stroke care' to 'standard stroke care' alone, available in study centres with access to specialist stroke units and set protocols for managing acute strokes. We define 'standard stroke care' as equal access to thrombolysis (intravenous or intra-arterial), thrombectomy, antiplatelet agents, and treatment in a specialist stroke unit. These interventions have been shown to affect both mortality and morbidity in acute stroke.

Types of outcome measures

We will assess mortality, disability, degree of temperature reduction and adverse effects.

Primary outcomes

- Poor functional outcome (modified Rankin Scale (mRS) $\geq$ 3) at final follow-up

We will calculate disability using the standardised, validated scoring system known as the modified Rankin Scale (mRS) to ensure consistency in assessing disability (Banks 2007). We will measure disability by dichotomising the results of the mRS into poor functional outcome (3 to 6) and free of significant disability (0 to 2) at the end of follow-up.

Secondary outcomes

- Mortality, measured dichotomously using the mRS obtained from point 6 on the mRS at the end of final follow-up
- Degree of temperature reduction, measured continuously from induction of cooling to the end of the cooling period
- Free of significant disability ('functionally independent', defined as a mRS of 0 to 2) at the end of final follow-up
- Adverse events (infections (chest and urine), cardiac arrhythmias, intra and extracranial bleeding), metabolic adverse events (glycaemia, oxygenation, and acid-base balance) at the end of final follow-up. We will collect bleeding and infection rates as defined and reported by trial investigators.

'Final follow-up' will be taken at the end of the longest follow-up period in the studies. We will record when the outcome was measured in different trials to ensure different follow-up periods are accounted for (e.g. at 1 month, > 1 month to 3 months, > 3 months).

Search methods for identification of studies

See the methods for the Cochrane Stroke Group 'Specialised register'. We will search for trials in all languages and arrange for the translation of relevant articles where necessary.

Electronic searches

We will search the Cochrane Stroke Group trials register and the following electronic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library; latest issue) in the Cochrane Library
- MEDLINE Ovid (from 1946) ([Appendix 1](#))
- Embase Ovid (from 1974)
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1982)
- BIOSIS Citation Index (from 1926)
- Web of Science: Science Citation Index Expanded (from 1900)
- Web of Science: Conference Proceedings Citation Index-Science (from 1990)

We will model the subject strategies for databases on the search strategy designed for MEDLINE by Cochrane Stroke's Information Specialist ([Appendix 1](#)). All search strategies deployed will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2011](#)).

We will also search the following ongoing trials registers.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/)
- World Health Organization (WHO) International Clinical Trials Registry Platform (who.int/ictrp/en/)
- Stroke Trials Registry (www.strokecenter.org/trials/)

Searching other resources

In an effort to identify further published, unpublished, and ongoing trials, we will:

- check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials;
- contact original authors for clarification and further data if trial reports are unclear;

- contact experts/trialists/organisations in the field to obtain additional information on relevant trials where necessary;
- conduct a search of various grey literature sources, dissertation and theses databases, and databases of conference abstracts.

Data collection and analysis

Selection of studies

Two review authors (AM, SR) will independently screen titles and abstracts of the references obtained as a result of our searching activities and will exclude obviously irrelevant reports. We will retrieve the full-text articles for the remaining references and two review authors (AM, SR) will independently screen the full-text articles and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (KG). We will collate multiple reports of the same study so that each study, not each reference, is the unit of interest in the review. We will record the selection process and complete a PRISMA flow diagram ([Moher 2009](#)).

Data extraction and management

Two review authors (AM, SR) will independently extract data from included studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (KG).

We will extract information for the following items.

- Basic trial characteristics: name, year, funding, conflicts of interest, and publication type.
- Participant characteristics: age, gender, type of stroke, severity, hours of onset of stroke symptoms, and method of stroke diagnosis (we will also check for baseline imbalances in patient characteristics across study groups).
- Intervention type: method, onset, duration and depth of temperature reduction.
- Comparison intervention characteristics.
- Outcome data: length and type of follow-up, dropouts, mortality, mRS and complications, such as rates of infections (chest and urinary), bleeding (intra and extracranial) and arrhythmias.
- Information needed for 'Risk of bias' assessment, including whether an intention-to-treat analysis was used.

Where missing information or unclear methods of reporting are found, we will contact authors to gain the original patient data.

Assessment of risk of bias in included studies

Two review authors (AM, SR) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (KG). We will assess the risk of bias according to the following domains.

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

We will grade the risk of bias for each domain as high, low, or unclear, and provide information from the study report together with a justification for our judgement in the 'Risk of bias' tables.

Measures of treatment effect

For the dichotomous outcomes - poor functional outcome, mortality, free from disability and complications - we will calculate risk ratios (RRs) and 95% confidence intervals (CIs) to summarise the effect for each trial. For the continuous variable - change in temperature - we will calculate the mean difference (MD) and a 95% CI for each trial.

Unit of analysis issues

In standard RCTs we will treat the participant as the unit of analysis. In the case of cluster-randomised controlled trials we will treat the cluster as the unit of analysis. We will extract, where available, a direct estimate of the required effect from an analysis that properly accounts for the cluster design. Where such data are unavailable, we will perform an assumed intraclass correlation if we can extract the required information (Higgins 2011).

Dealing with missing data

In the case of missing data, we will contact the study authors directly. If missing data are not provided, we will explore the effects of excluding the study in a sensitivity analysis.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity between studies to establish whether we think it is appropriate to pool studies in meta-analyses. If we carry out any meta-analyses we will use both a visual inspection of CIs and the I^2 statistic to calculate the degree of heterogeneity; where we will take an I^2 value of 50% as an indicator of moderate heterogeneity. We will use a random-effects model to analyse the data as there is likely to be

a degree of clinical heterogeneity given the multiple treatments eligible for inclusion (physical versus pharmacological cooling), and the potential duration and depths of cooling (Higgins 2003). We have prespecified sensitivity and subgroup analyses. However, if high levels of heterogeneity are observed ($\geq 80\%$) that are not explained by our prespecified subgroup and sensitivity analyses below, we will provide a narrative summary rather than report meta-analyses.

Assessment of reporting biases

Where 10 or more studies are included in a meta-analysis we will assess the potential for reporting bias using funnel plots and Egger's regression tests, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where possible, we will also assess whether recruitment of participants occurred before publication of the protocol, and whether the trial was registered on a clinical trials register.

Data synthesis

We will provide a narrative summary of the included studies, and where we consider studies to be sufficiently similar, we will conduct meta-analyses by pooling the appropriate data using Review Manager 5 (Review Manager 2014). For outcomes that provide dichotomous data, we will combine the RR and 95% CI from individual studies using random-effects Mantel-Haenszel models, to calculate the pooled overall RR with a 95% CI. For outcomes that provide continuous data, we will use a random-effects inverse variance model to calculate the pooled overall MD with a 95% CI.

GRADE and 'Summary of findings' table

We will create a 'Summary of findings' table including the following outcomes: poor functional outcome (mRS ≥ 3) at final follow-up; mortality, which will be measured using the mRS obtained from point 6 on the mRS at the end of final follow-up; degree of temperature reduction at induction of cooling and at 72 hours from induction; free of significant disability ('functionally independent' defined as a mRS of 0 to 2) at the end of final follow-up; and adverse events (infections (chest and urine), cardiac arrhythmias, intra and extracranial bleeding) at the end of final follow-up (Table 1).

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence contributing to each outcome (Atkins 2004). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEproGDT software (GRADEproGDT 2015). We will justify all decisions to downgrade the quality of studies using

footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We expect that the variables below may introduce heterogeneity into the analyses. We will perform the following prespecified subgroup analyses for the primary outcomes to investigate this.

- Pharmacological versus physical temperature reduction interventions (as the interventions vary significantly with a deeper hypothermic level induced in the physical cooling trials) (Den Hertog 2009b).
- Type and dose of pharmacological agent (to see if different medications and doses affect outcome).
- Duration of pharmacological temperature reduction intervention: (24 to 48 hours, 48 to 72 hours, or 72 to 120 hours).
- Studies that effectively cooled participants versus those that did not achieve cooling.

- Duration of physical cooling (12 to 24 hours, 24 to 72 hours, or 72 to 120 hours).
- Type of stroke (to assess if cooling preferentially affects mortality and disability in bleeding or ischaemic strokes).

Sensitivity analysis

We will carry out sensitivity analyses for the following parameters.

- Excluding studies judged to be at high risk of bias for any domain.
- Excluding studies with missing data, where this cannot be supplied by the study authors.

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We thank Cochrane Stroke for its support during the development of this protocol.

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. Summary of findings

Temperature reduction (cooling) compared with standard stroke care for acute stroke						
Patient or population: acute stroke Settings: inpatient Intervention: temperature reduction (cooling) to normothermia or hypothermic levels Comparison: standard stroke care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	Temperature reduction				
Poor functional outcome (mRS ≥ 3) at final follow-up (primary outcome)						
Mortality (measured from point 6 on the mRS) at final follow-up						
Degree of temperature reduction at induction of cooling and at 72 hours from induction						
Free of significant disability ('functionally independent' defined as a mRS of 0-2) at the end of final follow-up						
Adverse events (infections (chest and urine), cardiac arrhythmias, in-						

Table 1. Summary of findings (Continued)

tra and extracranial bleeding), metabolic adverse events (glycaemia, oxygenation and acid-base balance) at the end of final follow-up						
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval; mRS: modified Rankin Scale; RR: risk ratio</p> <p>GRADE Working Group grades of evidence</p> <p>High quality: further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: we are very uncertain about the estimate.</p>						

APPENDICES

Appendix I. MEDLINE search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke\$ or poststroke or apoplex\$ or cerebral vasc\$ or brain vasc\$ or cerebrovasc\$ or cva\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA\$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracran\$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli\$ or putaminal or putamen or posterior fossa or hemispher\$ or subarachnoid) adj5 (h?emorrhag\$ or h?ematoma\$ or bleed\$)).tw.
5. hemiplegia/ or exp paresis/ or exp Gait Disorders, Neurologic/
6. (hemipleg\$ or hemipar\$ or paresis or paraparesis or paretic).tw.
7. or/1-6
8. cryotherapy/ or hypothermia, induced/
9. (hypotherm\$ or cryotherap\$ or cold or cool\$ or temperature\$ or antipyretic).tw.
10. Hypothermia/
11. cold temperature/ or freezing/

12. or/8-11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. or/13-19
21. 7 and 12 and 20

CONTRIBUTIONS OF AUTHORS

Abid Malik is the guarantor and will draft the manuscript and will design, collect, and analyse the data and will write the review.

Nicola Lindson and Rachna Begh are supervisors for advice and direction.

Saleema Roze and Kelda Green will provide help with data extraction, resolution of disagreements, and study selection.

All authors will review drafts of the manuscript.

DECLARATIONS OF INTEREST

Abid Malik: none known

Nicola Lindson: none known

Rachna Begh: none known

Saleema Roze: none known

Kelda Green: none known

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