Systematic review of head cooling in adults after traumatic brain injury and stroke

B Harris,[1,2]* PJD Andrews,[2] GD Murray,[1] J Forbes[1] and O Moseley[3]

[1]School of Clinical Sciences and Community Health, University of Edinburgh, Edinburgh, UK
[2]NHS Lothian, Edinburgh, UK
[3]NHS Ayrshire and Arran, Ayr, UK

*Corresponding author

Executive summary

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Executive summary

Background

Brain injuries caused by stroke and trauma are common and costly in human and resource terms. The result of traumatic brain injury (TBI) and stroke is a cascade of molecular and physiological derangement, cell death, damage and inflammation in the brain. This, together with infection, if present, commonly results in patients having an increased temperature, which is associated with worse outcome. The usual clinical goal in TBI and stroke is therefore to reduce temperature to normal, although achieving this can be difficult. Temperature may sometimes be reduced to below normal (hypothermia) to reduce swelling if brain pressure is increased. However, research evidence does not yet conclusively show whether or not cooling patients after TBI and stroke improves their longer-term outcome (reduces death and disability). It is possible that complications of cooling outweigh the benefits.

Cooling methods can be classified into those that cool the whole body (systemic cooling) and those targeted at the head to cool the brain directly. They include invasive and non-invasive techniques. Non-invasive head cooling is the subject of this review and these methods are categorised into:

- *heat loss from the upper airways* by convection with gas or fluid flow or by conduction with nasal or pharyngeal balloons
- *heat loss through the skull* by convection (fanning, hoods delivering cold air or water) or by conduction (*passive*, e.g. ice, gel caps or *active*, e.g. liquid cooling).

In current clinical practice, cooling methods are most commonly delivered systemically. But the logic behind head cooling is that it targets cooling where it is needed because it is brain temperature, rather than body temperature, which is important for brain protection. It is also thought that brain cooling may reduce the complications of hypothermia because relatively less body temperature reduction is required, although the evidence for this is not robust.

Existing systematic reviews of cooling interventions after TBI and stroke have not differentiated between cooling methods. We conducted this review to see if head cooling is effective in brain injury and stroke.

Aim and objectives

The aim was to assess the effectiveness and cost-effectiveness of non-invasive head cooling in adults after TBI and stroke, and provide a comprehensive assessment of head cooling research in these patients.

The objectives were to:

1. assess the effect of non-invasive head cooling on intracranial temperature (measured inside the skull and within the dura) and/or core body temperature (measured in an artery, the oesophagus, bladder or rectum)
2. assess the impact of non-invasive head cooling on disability, assessed with a validated outcome score, and mortality

3. determine adverse effects or complications associated with head cooling or the specific devices and methods used
4. assess the cost-effectiveness of head cooling in TBI and stroke
5. present the review results to members of the general public, in order to hear their views on the concept and possible use and effectiveness of head cooling.

Review methods

Criteria for inclusion of studies

Studies or case reports of any kind, in adults with TBI or stroke of any severity, using any form of non-invasive head cooling, were relevant. Studies of head cooling in cardiac arrest and neonatal hypoxic–ischaemic encephalopathy (HIE), conditions in which head cooling has been more commonly used, were also included if they had information on temperature reduction (cardiac arrest) or adverse effects of cooling methods and devices (cardiac arrest and neonatal HIE).

Studies in which head cooling was used solely during surgery or combined with another cooling intervention, excepting antipyretic drugs (e.g. paracetamol), were not relevant.

Search methods

The searches were not restricted by publication status, date or language. The following databases and resources were searched using a wide variety of terms related to head/brain *and* cooling/hypothermia plus condition-specific terms. Dates are for the most recent search.

Major international medical bibliographical databases

MEDLINE 1950 to 12 March 2011.
OLDMEDLINE 1948–65.
EMBASE 1980 to 2011 Week 10.
EMBASE Classic 1947–79.
Cumulative Index of Nursing and Allied Health Literature (CINAHL) 1937 to April 6 2010.
British Nursing Index and Archive 1985 to May 2010.
Web of Science Conference Proceedings Citation Index-Science 1990 to 19 July 2010.
Zetoc Conference Proceedings (8 August 2010).
ProQuest Dissertations & Theses (PQDT) database (25 March 2011).

The Cochrane Library

Cochrane Central Register of Controlled Trials (2011 Issue 1).
Cochrane Database of Systematic Reviews (2011 Issue 3).
Database of Abstracts of Reviews of Effects (2011 Issue 1).
Health Technology Assessment Database (2011 Issue 1).
NHS Economic Evaluation Database (2011 Issue 1).

Cochrane specialised trials registers

Cochrane Injuries Group (14 June 2010).
Cochrane Stroke Group (5 May 2010).

Other trial registers (last update all registers 6 March 2011)

World Health Organization International Clinical Trials Registry Platform.
Current Controlled Trials: the meta-register of controlled trials and International Standard Randomised Controlled Trial Number (ISRCTN) register.
ClinicalTrials.gov.
National Research Register archive.
Stroke Trials Registry.

Country-specific databases

Informit Health Collection (includes Australasian Medical Index) (6 February 2011).
China National Knowledge Database: China Academic Journals Medicine and Public Health (hygiene) database (14 January 2011).
Japan Science and Technology Agency: J-EAST (16 August 2010), J-STAGE (5 February 2011), journal@rchive (4 February 2011).
Latin American Caribbean Health Sciences Literature (5 February 2011).
Russian Academy of Sciences Bibliographies (25 March 2011).

Web search engines

Scirus (7 March 2011).
Google Scholar (26 March 2011).

Reference lists of relevant studies and reviews and of books on therapeutic hypothermia and the proceedings of hypothermia conferences were checked. Investigators and manufacturers of head-cooling equipment were contacted in writing.

Data collection and analysis

BH conducted the searches, with advice and help from the Cochrane Stroke Group Trials Search Co-ordinator. All retrieved results were imported into Reference Manager (version 11, Thomson Reuters, CA, USA), de-duplicated, and titles and abstracts screened to remove anything that did not meet the review criteria. Where full review or further information to determine relevance was required the complete paper was obtained and screened. This resulted in a final data set of studies that met the review criteria, with full text where this existed, for detailed assessment regarding inclusion and exclusion for analysis. From the final data set any studies that purported to be randomised controlled trials (RCTs) were independently assessed for quality by BH and PA. An intensive care doctor who spoke Chinese helped with papers in Chinese.

Only good-quality RCTs were prespecified for inclusion for formal analysis of patient outcome. All studies (including proof-of-concept and case studies) that contained information on head-cooling devices and methods, their efficacy in reducing temperature, ease of use and adverse effects were included for descriptive reporting. Temperature, being a physical measure of a physiological variable, was considered less susceptible to interpretation, even if, as was likely, full blinding was not possible given the nature of the intervention.

We were unable to carry out the analysis plan specified in the protocol because we found no good-quality RCTs that were suitable for inclusion in formal outcome analysis. Therefore, the results are presented descriptively.

Results

There were 46 studies (with 52 associated reports) in TBI, stroke and brain injury (mixed TBI and stroke population). There were 12 studies (15 reports) in cardiac arrest and 23 studies in neonatal HIE.

Effect of head cooling on temperature

Twelve studies had useable data on the effect of head cooling on intracranial and/or core body temperature data. Five were RCTs: one in TBI, two crossover trials in brain injury and two in cardiac arrest. The other seven were descriptive reports: two in stroke, three in brain injury and two in cardiac arrest.

The temperature data were simply tabulated because there was no straightforward method of presentation that addressed all of the sources of heterogeneity (e.g. different patient populations, reasons for cooling, method – upper airways or skull heat loss – and duration of cooling). Two of the studies showed no effect of head cooling on temperature. Replication of normal nasal airflow in intubated, brain-injured patients for 6 hours and ice packs to the head for 5–30 minutes in patients after cardiac arrest who were already cool (mean oesophageal temperature ≤ 35.5 °C). But otherwise the data showed that liquid head-cooling devices and an intranasal cooling device could reduce temperature by around 1 °C or more, within 1 hour. This is promising and, in particular, suggests that there may be a role for liquid head-cooling devices for induction and maintenance of modest temperature reduction in TBI and stroke (the intranasal cooling device was not designed for prolonged use). It was noteworthy that even in the presence of active body warming (applied to prevent head cooling having a 'knock-on' effect on body temperature), intracranial temperature was reduced with a liquid head-cooling device and could be reduced below core body temperature.

Effect of head cooling on outcome

We prespecified that only good-quality RCTs with blinded outcome assessment would be used to assess functional outcome and mortality. We were unable to establish that any of the trials with control groups met these criteria. Two RCTs were ineligible because they had a crossover design to assess proof of concept of intracranial temperature reduction with cooling consequently applied for short periods only. Otherwise, reasons included insufficient information on methods, outcome assessments that did not meet the review criteria and had either unblinded outcome assessment or insufficient information to determine if outcome assessment was blinded.

Adverse effects of head-cooling methods

All information on cooling method or device-related adverse effects that could be found in included or excluded studies, in studies in neonatal HIE, reviews of head cooling or in other applications of head cooling was included. Provided that the devices were used correctly and contraindications were observed, side effects from the cooling methods were generally minor and were resolved without treatment after cooling stopped. They included whitening of the nose from cold (with the intranasal device) and small areas of skin damage.

Complications and possible benefits: head cooling compared with systemic cooling

We found no high-quality RCT evidence on the relative complications and benefits of head cooling compared with systemic cooling in TBI and stroke, or cardiac arrest.

Modelling of cost-effectiveness of head cooling

The review searches produced no suitable data for economic modelling and therefore this was unable to be undertaken. However, we did create an exploratory model of possible treatment effects and the cost-effectiveness of head cooling using local data for patients with TBI. The insight gained from the modelling was inevitably limited because of the lack of outcome data with head cooling. The model took the Glasgow Coma Scale score as a rough proxy for how severely injured a patient was and suggests that, if head cooling could reduce length of stay, there may be a substantial reduction in costs as the location in which the treatment is given (critical care) is very expensive.

However, the main benefit of head cooling for TBI is proposed to be improving the quality of life and reducing disability over the patient's lifetime. We found, somewhat surprisingly, that data on the lifetime costs of TBI are not available in the UK, and therefore it was not possible to directly

assess the long-term cost. As a result, steps are now being taken in Scotland to address this and we are working with a group of people under the auspices of the Acquired Brain Injury Managed Clinical Network to improve data collection on patients with TBI. Nevertheless, extrapolating from UK data on lifetime health- and social-care costs for people aged > 65 years, which are high, does suggest that if head cooling can positively impact on the quality of life for TBI patients then the intervention may be cost-effective.

Public involvement

In the UK, to date, head cooling in adults has been a research intervention and not part of normal clinical care. As a result, there have been very few service users of head cooling. Those patients who have had head cooling were critically ill, sedated and unconscious, with, consequently, very limited or no awareness of the intervention. On the other hand, almost any member of the public might be a potential service user in the future, and be thrust into that situation without prior warning because head cooling is an acute intervention for sudden and unexpected health emergencies. Therefore, during preparation of the report, the results of the review were presented to members of the general public in order to give them an opportunity to comment on and discuss the concept, possible use and effectiveness of head cooling, and also issues of consent for research when people were too ill to consent for themselves. Those involved appreciated that this kind of research might be something that people could be confronted with 'out of the blue' and thought it was important that this was more widely known.

Conclusions

We found a larger number of studies than expected but few RCTs of confirmable quality and none that allowed us to determine if head cooling improves functional outcome. The review has shown that some methods of head cooling can reduce intracranial temperature, which is an important first step in determining effectiveness, but the evidence is not robust.

Recommendations for research in traumatic brain injury and stroke

1. We suggest that active head-cooling devices are the most promising for further research.
2. More robust proof of concept of temperature reduction with head cooling is required. The effectiveness of head cooling in achieving and maintaining both normothermia and hypothermia should be assessed. Intracranial temperature should be measured (whenever feasible), as well as core trunk temperature in the oesophagus (or pulmonary artery), otherwise bladder, with rectal temperature a last resort. It should be absolutely clear in study reports whether temperature has changed with cooling and by how much. Baseline temperatures, duration of cooling, temperatures achieved with cooling, and temperature change with cooling should be reported, with measures of central tendency and spread.
3. Head cooling, with and without body warming, should be compared with systemic cooling to determine if complications, including shivering, infection and coagulation abnormalities, are fewer.
4. In volunteers the effect on brain temperature gradients of different methods of head cooling with and without body warming might be assessed with magnetic resonance spectroscopy temperature measurement.
5. Head cooling as a method of treating raised intracranial pressure should be investigated.
6. The efficacy of head-cooling methods in maintaining cooling after induction of therapeutic hypothermia with cold intravenous fluids should be assessed.

7. The tolerability and effectiveness (infection, shivering, temperature reduction, functional outcome) of head cooling in achieving normothermia and hypothermia in awake patients should be assessed.
8. In stroke patients the effect of head cooling prior to, and during, thrombolysis should be evaluated.
9. In stroke, the efficacy and tolerability of intranasal cooling combined with external head cooling should be investigated (intranasal cooling may not be suitable for trauma patients).

Implications for practice in traumatic brain injury and stroke

1. Head cooling has potential as a means of reducing raised intracranial temperature when this is clinically indicated, but there is insufficient evidence to recommend its use outside of research trials.
2. Improved methods of recording and tracking patients after TBI are required throughout the UK in order that the impact and costs can be measured.

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Publication

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NIHR Health Technology Assessment programme

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/37/32. The contractual start date was in May 2009. The draft report began editorial review in June 2011 and was accepted for publication in November 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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