Hypothermia for traumatic head injury (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

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[Intervention Review]

Hypothermia for traumatic head injury

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Editorial group: Cochrane Injuries Group.
Publication status and date: Edited, conclusions changed, published in Issue 1, 2009.
Review content assessed as up-to-date: 22 May 2008.

Citation: Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD001048. DOI: 10.1002/14651858.CD001048.pub3.

ABSTRACT

Background

Hypothermia has been used in the treatment of head injury for many years. Encouraging results from small trials and laboratory studies led to renewed interest in the area and some larger trials.

Objectives

To estimate the effect of mild hypothermia for traumatic head injury on mortality and long-term functional outcome complications.

Search strategy

We searched the Injuries Group Specialised Register, Current Controlled Trials *Meta*Register of trials, Zetoc, Web of Knowledge; Science Citation Index [expanded], CENTRAL, MEDLINE and EMBASE. We handsearched conference proceedings and checked reference lists of relevant articles. The search was updated on 23 May 2008.

Selection criteria

Randomised controlled trials of hypothermia to a maximum of 35ºC for at least 12 hours versus control in patients with any closed traumatic head injury requiring hospitalisation. Two authors independently assessed all trials.

Data collection and analysis

Data on death, Glasgow Outcome Scale and pneumonia were sought and extracted, either from published material or by contacting the investigators. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each trial on an intention-to-treat basis.

Main results

We found 22 trials with a total of 1409 randomised patients. Twenty trials involving 1382 patients reported deaths. There were fewer deaths in patients treated with hypothermia than in the control group (OR 0.76, 95% CI 0.60 to 0.97). Eight trials with good allocation concealment showed a non-significant reduction in the likelihood of death for patients treated with hypothermia (OR 0.96, 95% CI 0.68 to 1.35). Twenty trials involving 1382 patients reported data on unfavourable outcomes (death, vegetative state or severe disability). Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.69, 95% CI 0.55 to 0.86). Eight trials with good allocation concealment showed a non-significant reduction in the likelihood of unfavourable outcome for patients treated with hypothermia (OR 0.79, 95% CI 0.57 to 1.08). Hypothermia treatment was associated with an increase in odds of pneumonia but this increase was not statistically significant for trials with good allocation concealment (3 trials, 69 patients, OR 1.06, 95% CI 0.38 to 2.97).

Authors' conclusions

Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. Low quality trials have a tendency to overestimate the treatment effect. The high quality trials found some statistically non-significant benefit of hypothermia which could be due to the play of chance. Hypothermia may increase the risk of pneumonia. Due to uncertainties in its effects, hypothermia should only be given to patients taking part in a randomised controlled trial with good allocation concealment.

PLAIN LANGUAGE SUMMARY

Hypothermia (body temperature cooling) for traumatic head injury

Twenty-two randomised controlled trials involving 1409 patients with traumatic head injury were included in this review. In each trial, the patients were randomly divided into two groups: one group remained at normal body temperature, and the other group was cooled to a maximum of 35 degrees Celsius for at least 12 hours. Cooling could be of the whole body (e.g. with a blanket with circulating cold water), or just the head (e.g. with a helmet with circulating cold water). Information on death, disability, and pneumonia was evaluated for each trial.

The review authors found that fewer people died or became severely disabled if they were treated with hypothermia, but this finding may be due to the play of chance. It was also found that patients given hypothermia were more likely to develop pneumonia, and some patients died from pneumonia, but the increased risk of pneumonia could also be due to the play of chance.

Some of the trials included in the review were of low methodological quality. Low quality trials have a tendency to overestimate the effect of a treatment. In this review, the lower quality trials showed hypothermia treatment to be effective in reducing death and disability among head injured patients. However, the good quality trials showed less benefit for hypothermia treatment and a lower chance of pneumonia.

The review authors conclude that hypothermia might reduce death and disability in traumatic head injured patients, but it may also increase the risk of pneumonia. These effects may be due to the play of chance. Due to uncertainties in its effects, hypothermia should only be given to patients taking part in good quality randomised controlled trials.

BACKGROUND

Traumatic head injury is a major cause of death and disability amongst a predominantly young population, with an estimated ten million people experiencing severe head injury worldwide every year (Alexander 1992). There is, however, a significant lack of evidence about effective therapies in the acute care of these patients. A long-term effort to review the literature and produce management guidelines by the American Association of Neurological Surgeons (Bullock 1996; Kirkpatrick 1997) could only make four definitive statements about treatment effectiveness that were supported by strong evidence from randomised studies.

Mild to moderate hypothermia has been used in the treatment of head injury for over 50 years (Fay 1945). Although there were several promising experimental studies (Laskowski 1960; Clasen 1968) and case series (Sedzimir 1959; Shapiro 1974), no controlled clinical studies were performed and the therapy fell from favour. In the last decade, however, several investigators have reported encouraging results of Phase II and III randomised clinical trials (Clifton 1995; Marion 1997; Shiozaki 1993), corroborated by consistent findings of high levels of cerebral protection associated with systemic cooling in well validated laboratory models of global ischaemia (Busto 1987). The early trials were small, single-centre investigations, which were sufficiently promising to lead on to larger, multi-centre trials.

Whilst the mechanism of action of such temperature control therapy was originally thought to be primarily a reduction in cerebral metabolic rate (Bering 1961), there is now evidence that mild hypothermia might also influence the excessive post-traumatic release of excitatory neurotransmitters (Busto 1989), and attenuate the opening of the blood-brain barrier (Smith 1996). The main risks associated with induced systemic hypothermia are an increased risk of sepsis and pneumonia, coagulation abnormalities, and pos-

sible myocardial ischaemia and atrial fibrillation (Schubert 1995).

OBJECTIVES

To determine whether the use of mild hypothermia in the treatment of traumatic head injury:

- reduces the risk of death (either during the treatment period or at the end of follow-up);
- reduces the proportion of patients who at final follow-up are either dead, in a vegetative state, or severely disabled;
- increases the risk of pneumonia.

METHODS

Criteria for considering studies for this review

Types of studies

A search was conducted for all randomised controlled trials of mild hypothermia versus control.

Types of participants

Patients with any closed traumatic head injury requiring hospitalisation.

Types of interventions

Therapeutic cooling, either locally or systemically, by means of a fluid-filled cooling blanket, a 'bear-hugger' air-cooling device, ice water lavage, any combination of the above, or other methods, to a target temperature of at most 35°C for a period of at least 12 consecutive hours. Cooling could begin immediately upon admission to the intensive therapy unit or be deferred until ICP becomes uncontrollable by conventional management.

Types of outcome measures

Primary outcomes

- All-cause mortality at the end of the follow-up period.
- Unfavourable outcome at the end of the follow-up period.

Unfavourable outcome was defined as a Glasgow Outcome Scale score of 'severe disability', 'persistent vegetative state', or 'death'; or an equivalent measure if a Glasgow Outcome Score was not presented.

Secondary outcomes

- The frequency of pneumonia.

Search methods for identification of studies

None of the searches were restricted by language, date or publication status.

Electronic searches

For the initial version of the review we searched The Cochrane Injuries Group's Specialised Register in May 1998 for any relevant randomised trials relating to temperature control using the search terms: hypotherm* OR normotherm* OR cool* OR cold* OR temperature.

The search strategy for the register is primarily an electronic search of both MEDLINE and CENTRAL, supplemented by various hand-searching activities listed in the Group details. This was supplemented by a comprehensive EMBASE search, also performed in May 1998, to identify all potential RCTs involving human head injury and temperature control from 1980 onwards. Titles and abstracts from this search were reviewed by David Signorini for possibly relevant trial reports, and the appropriate articles retrieved. The original search strategies can be obtained by contacting the Trials Search Co-ordinator of the Cochrane Injuries Group.

Searches have since been carried out in October 2003, November 2005 and May 2008. The latest search strategies are listed in full in Appendix 1.

Searching other resources

The searches were supplemented by further handsearching of conference proceedings and abstracts as follows:

- International Conference on Recent Advances in Neurotraumatology, Italy 1996
- 2nd International Neurotrauma Symposium, Glasgow 1993
- 3rd International Neurotrauma Symposium, Toronto 1995
- 4th International Neurotrauma Symposium, Seoul 1997
- 27th Meeting of the Society for Critical Care Medicine, USA 1998
- 10th International Symposium on Intracranial Pressure, USA 1997

In addition, reference lists of all relevant trials and review articles were checked, and leading investigators in the field were contacted for information about any other published or unpublished trials which may have been overlooked.

Data collection and analysis

Selection of studies

The results of the search were screened by ES and IR. The full text of relevant records were obtained. Both authors independently compared the trial design with the inclusion criteria for this review. Disagreements were resolved by discussion.

Data extraction and management

The following information was extracted from each trial: method of allocation concealment, blinding of outcome assessment, number of randomised patients, death or severe disability at various times during follow up, treatment duration, duration of follow up, loss to follow up, and number of patients with pneumonia during the treatment period. This information was extracted and entered into Review Manager (RevMan) by ES; IR checked for accuracy. Trial report authors were contacted for additional information or clarification.

Assessment of risk of bias in included studies

Quality of allocation concealment was assessed by the review authors on the following scale (Higgins 2008):

- Yes: low risk of bias (e.g. sequentially numbered, sealed, opaque envelopes)
- No: high risk of bias (e.g. day of the week)
- Unclear: unclear or unknown risk of bias (method not stated).

Data synthesis

Mantel-Haenzel odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for death, pneumonia, and unfavourable outcomes for each trial on an intention-to-treat basis. The odds ratio was chosen because of the large variation in baseline event rates between the trials (mortality in the control groups ranges from 0% to 82%), implying that the relative risk would not be a good summary measure. Also, the Mantel-Haenzel approach was used because of the inaccuracy of Peto's approximation when the estimated treatment effect is large, as it was in several of the trials considered. Heterogeneity of treatment effect between trials was assessed using a standard chi-square test, I^2, and if appropriate, a weighted estimate of the typical treatment effect across all studies was calculated.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed to determine whether the treatment effect varies with: a) trial quality (quality of allocation concealment), b) duration of hypothermia, and c) length of follow-up.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting assessment; Characteristics of ongoing studies.

Results of the search

A total of 22 randomised controlled trials were identified that met the inclusion criteria.

Included studies

The 22 included randomised controlled trials involved 1409 randomised patients. All trials except two (Ishikura 1998, Meissner 2003a) reported the number of deaths in the intervention and control groups at final follow-up. Fourteen trials reported GOS scores specifically at three, six or 12 months post-injury. The occurrence of pneumonia was reported in ten trials.

Risk of bias in included studies

Allocation

Adequate allocation concealment is an important dimension of trial quality.

Eight trials had a reasonable standard of allocation concealment (Adelson 2005 HYPO1; Adelson 2005 HYPO2; Clifton 1992; Clifton 1993; Clifton 2001; Marion 1997; Meissner 1998; Qiu 2007). Twelve trials had unclear allocation concealment (e.g. 'by lot') (Aibiki 2000; Biswas 2002; Hashiguchi 2003; Hirayama 1994; Jiang 2000; Meissner 2003b; Shiozaki 1993; Shiozaki 1999; Shiozaki 2001; Smrcka 2005; Yan 2001; Zhang 2000). Two trials did not present mortality or GOS data in the treatment and control groups (Ishikura 1998; Meissner 2003a) and had unclear allocation concealment.

Effects of interventions

Death at final follow-up

Analysis 1.1

Twenty trials involving 1382 patients reported deaths. Patients treated with hypothermia were less likely to die than those in the control group (OR 0.76, 95% CI 0.60 to 0.97). There was no evidence of statistical heterogeneity between trials (Chi^2 = 15.53, df = 18 (P = 0.63); I^2 = 0%).

Death at final follow-up stratified by trial quality

Analysis 1.2

Concealed allocation was reported in 8 studies involving 686 patients. Hypothermia treatment was associated with a statistically non-significant reduction in death compared with the control group (OR 0.96, 95% CI 0.68 to 1.35). There was no evidence of statistical heterogeneity between trials (Chi^2 = 1.01, df = 7 (P = 0.99); I^2 = 0%).

Non-concealed allocation, or 'unclear' concealment according to Higgins 2008, was reported in 12 studies involving 696 patients. Patients treated with hypothermia were less likely to die than those in the control group (OR 0.62, 95% CI 0.44 to 0.86). There was no evidence of statistical heterogeneity between trials (Chi^2 = 11.14, df = 10 (P = 0.35); I^2 = 10%).

Unfavourable outcome at final follow-up

Analysis 1.3

Twenty trials involving 1382 patients reported death or severe disability. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.69, 95% CI 0.55 to 0.86). There was some evidence of statistical heterogeneity between trials (Chi^2 = 30.71, df = 19 (P = 0.04); I^2 = 38%).

Unfavourable outcome stratified by trial quality

Analysis 1.4

Concealed allocation was reported in 8 studies involving 686 patients. Hypothermia treatment was associated with a statistically non-significant reduction in death compared with the control group (OR 0.79, 95% CI 0.57 to 1.08). There was no statistical heterogeneity between trials (Chi^2 = 4.79, df = 7 (P = 0.69); I^2 = 0%).

Non-concealed allocation, or 'unclear' concealment according to Higgins 2008, was reported in 12 studies involving 696 patients. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.60, 95% CI 0.44 to 0.82). There was some statistical heterogeneity between trials (Chi^2 = 24.64, df = 11 (P = 0.01); I^2 = 55%).

Unfavourable outcome stratified by treatment duration

Analysis 1.5

Twelve trials reported deaths or severe disability according to the duration of treatment.

Two trials involving 91 patients treated patients in the hypothermia group for 24 hours. Patients in the hypothermia group were less likely to have an unfavourable outcome than those in the control group (OR 0.38, 95% CI 0.16 to 0.90). There was no statistical heterogeneity between these two trials (Chi^2 = 0.00, df = 1 (P = 0.99); I^2 = 0%).

Ten trials involving 683 patients treated patients in the hypothermia group for 48 hours. Hypothermia treatment was associated with a statistically non-significant reduction in unfavourable outcome compared with the control group (OR 0.96, 95% CI 0.70 to 1.31). There was no statistical heterogeneity between trials (Chi^2 = 12.13, df = 9 (P = 0.21); I^2 = 26%).

Unfavourable outcome at various times during follow-up

Analysis 1.6

Fourteen trials reported GOS scores at three, six or 12 months post-injury. Some trials reported GOS scores at more than one time point.

Six trials involving 271 patients reported GOS scores at three months post-intervention. Hypothermia treatment was associated with a statistically non-significant reduction in death compared with the control group (OR 0.85, 95% CI 0.52 to 1.39). There was some statistical heterogeneity between trials (Chi^2 = 10.29, df = 5 (P = 0.07); I^2 = 51%).

Eight trials involving 634 patients reported GOS scores at six months post-intervention. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.62, 95% CI 0.45 to 0.86). There was significant statistical heterogeneity between trials (Chi^2 = 21.55, df = 7 (P = 0.003); I^2 = 68%).

Four trials involving 262 patients reported GOS scores at 12 months post-intervention. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.52, 95% CI 0.31 to 0.87). There was no statistical heterogeneity between trials (Chi^2 = 3.62, df = 3 (P = 0.31); I^2 = 17%).

Pneumonia during the treatment period

Analysis 1.7

Ten trials involving 322 patients reported pneumonia cases. Patients treated with hypothermia were more likely to have pneumonia than those in the control group (OR 2.06, 95% confidence interval 1.28 to 3.30).

Pneumonia was stratified by trial quality:

Three trials with good allocation concealment involving 69 patients reported pneumonia cases. Hypothermia treatment was associated with a statistically non-significant increase in pneumonia (OR 1.06, 95% confidence interval 0.38 to 2.97). There was no statistical heterogeneity between trials (Chi^2 = 0.55, df = 2 (P = 0.76); I^2 = 0%).

Seven trials with non-concealed allocation involving 253 patients reported pneumonia cases. Patients treated with hypothermia were more likely to have pneumonia than those in the control group (OR 2.47, 95% confidence interval 1.44 to 4.23). There was no statistical heterogeneity between trials (Chi^2 = 9.34, df = 5 (P = 0.10); I^2 = 46%).

DISCUSSION

Summary of main results

Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. The high quality trials found some statistically non-significant benefit of hypothermia which could be due to the play of chance. Hypothermia may increase the risk of pneumonia. Due to uncertainties in its effects, hypothermia should only be given to patients taking part in a randomised controlled trial with good allocation concealment.

Quality of the evidence

Numerous trials of hypothermia treatment have been conducted in recent years. The majority of trials found were of low quality, with unclear allocation concealment. These low quality trials may overestimate the effectiveness of hypothermia treatment versus control.

Trials with good allocation concealment showed a smaller treatment effect which may be due to the play of chance. The increased incidence of pneumonia was not statistically significant in trials with good allocation concealment.

Potential biases in the review process

This systematic review addresses a focused research question using predefined inclusion criteria and methodology to select and appraise eligible studies.

As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching we believe that the risk of such a bias affecting the results is minimal.

The majority of trials found or included in the review were of low methodological quality. An additional ten trials with unclear methods of randomisation or allocation concealment were identified, and are awaiting assessment until clarification is obtained from the trial report authors.

Agreements and disagreements with other studies or reviews

The conclusions of this review are broadly consistent with those of Peterson 2008. The majority of trials identified for this review and Peterson 2008 were of low methodological quality. Both reviews found there may be an increased likelihood of pneumonia with hypothermia.

AUTHORS' CONCLUSIONS

Implications for practice

Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. Low quality trials have a tendency to overestimate the treatment effect. The high quality trials found some statistically non-significant benefit of hypothermia which could be due to the play of chance. Hypothermia may increase the risk of pneumonia. Due to uncertainties in its effects, hypothermia should only be given to patients taking part in a randomised controlled trial with good allocation concealment.

Implications for research

More high quality randomised controlled trials are needed to determine the benefit of hypothermia for traumatic head injury.

ACKNOWLEDGEMENTS

Thanks to:

- Brenda Thomas (Stroke Review Group) for help and advice with the original EMBASE search strategy.
- Ian Whittle, Kate Signorini, Elena Telaro, Yoichi Nagayama, Irene Kwan, Frank Del Vecchio, Lisa Xue and Cynthia To for help with manuscripts in languages other than English.
- Reinhard Wentz and Irene Kwan of the Injuries Group for the original searches.
- Katharine Ker of the Injuries Group for work on previous versions of the review.
- Karen Blackhall, Trials Search Co-ordinator of the Cochrane Injuries Group for updating the searches in 2003, 2005 and 2008.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adelson 2005 HYPO1

Methods	Multicentre, randomised, controlled trial.
Participants	Patients less than 13 years of age, with a GOS of 8 or less.
Interventions	Hypothermia patients: Cooling to 32-33C within 6 hours of injury for 48 hours. Passively rewarmed by 1C every 3-4 hours. Normothermia patients: no intervention/not reported.
Outcomes	ICP CPP Mortality Infection Arrhythmia Coagulopathy Pneumonia
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	'The investigators were blinded to the allocation. The statistician and data systems manager controlled the randomisation protocol and were blinded to the site.' Adelson 2008b

Adelson 2005 HYPO2

Methods	Single centre, randomised, controlled trial.
Participants	Patients less than 17 years of age, with a GOS of 8 or less.
Interventions	Hypothermia patients: Cooling to 32-33C for 48 hours. Passively rewarmed by 1C every 3-4 hours. Normothermia patients: no intervention/not reported.
Outcomes	ICP CPP Mortality Infection Arrhythmia Coagulopathy Pneumonia

Adelson 2005 HYPO2 (*Continued*)

Notes	The time between injury and randomisation was more than 6 hours. In some cases there was an unknown time of injury (e.g. child abuse)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	'The investigators were blinded to the allocation. The statistician and data systems manager controlled the randomisation protocol and were blinded to the site.' Adelson 2008b

Aibiki 2000

Methods	Randomised controlled trial. Four patients were excluded from the normothermic group after randomisation because of abdominal or chest injuries
Participants	Patients aged 4 to 76, within 8 hours of traumatic brain injury. Glasgow coma scale score of 8 or less on admission to emergency room
Interventions	Hypothermia patients: Cooling to 32-33C within 4 hours on injury for 3-4 days. Rewarming at 1C per day. Normothermia patients: maintained at 36-37C.
Outcomes	Death and GOS at 6 months. Thromboxane A2 and prostaglandin I2 levels during study. Complications during treatment
Notes	GOS assessed by "independent neurosurgeon who were not aware of the study". p.3904

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	'Patients were assigned randomly to each group.' p. 3903 No mention of allocation concealment

Biswas 2002

Methods	Randomised controlled trial.
Participants	Children up to 18 years old, with closed traumatic brain injury and a GCS of 8 or less
Interventions	Hypothermia patients (n=10): cooled to 32 to 34 degrees Celsius for 48 hours, by cooling blanket placed underneath the body. Rewarming over a period of 12 hours. Control patients (n=11): rectal temperature was maintained between 36.5 and 37.5 degrees Celsius

Biswas 2002 (*Continued*)

Outcomes	Death. GOS at three, six and 12 months. ICP and CPP.
Notes	GOS assessed blind to allocation. Analysis on an intention-to-treat basis. Two patients in the hypo group were lost to follow-up and the end of the study period. (2/10 lost to follow-up.) Five patients in the control group were lost to follow-up at the end of the study period. (5/11 lost to follow-up.)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Clifton 1992

Methods	Randomised controlled trial.
Participants	Patients with GCS 4-8 with closed head injury but no major systemic injuries, in whom cooling could begin within 6 hours of injury
Interventions	Hypothermia patients: cooling to 30-32C for 24 hours using cooling blankets and iced saline stomach lavage. Rewarming over a period of 24 hours. Control patients: No active temperature management.
Outcomes	Death and GOS at 3 months. Complications during treatment phase.
Notes	GOS was not assessed blind to treatment allocation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	By 'sealed envelopes'.

Clifton 1993

Methods	Randomised controlled trial.
Participants	Patients age 16 to 60, GCS 4-7 with closed head injury but no major systemic injuries, in whom cooling could begin within 6 hours of injury

Clifton 1993 (*Continued*)

Interventions	Hypothermia patients: cooling to 32-33C for 48 hours using cooling blankets. Rewarming over a period of 48 hours. Control patients: Cooling blankets were used to maintain body temperature at 37C for 80 hours
Outcomes	Death and GOS at 3 months. Complications during treatment period. ICP during treatment period.
Notes	GOS assessed blind to treatment allocation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	By 'sealed envelopes'.

Clifton 2001

Methods	Randomised controlled trial.
Participants	Patients aged 16 to 65 with a non-penetrating head injury and a Glasgow coma scale of 3 to 8 after resuscitation
Interventions	Hypothermia patients: cooling to 32.5-34C for 48 hours using ice, cold gastric lavage, unwarmed ventilator gases, and then temperature control pads. Rewarming at rate of up to 0.5C in 2 hours. Control: Body temperature maintained at 37C.
Outcomes	Death and GOS at 6 months. ICP monitored during treatment. Nine neurobehavioural and neuropsychological scales at 6 months
Notes	GOS was assessed blind to treatment allocation. Outcome data missing for 7 patients, and not presented for 17 patients whose entry details were incomplete

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Allocation concealment unclear, but report states that "only the study biostatistician was aware of each patient's treatment group assignment"

Hashiguchi 2003

Methods	Randomised controlled trial. Allocation method not stated.
Participants	Participants age 10 years or older, with a GCS of 8 or less, 'who required continuous infusion of barbiturates to control intracranial hypertension.' p.1055
Interventions	Hypothermia patients (n=9): intracranial temperature in the lateral ventricle was maintained at 33.5 to 34.5 degrees Celsius for 48 hours, by water circulating blankets above and below the body. Rewarming over a period of 3 days, by 1 degree Celsius each day. Control patients (n=8): intracranial temperature was maintained between 36.5 and 37.5 degrees Celsius for 5 days, by water circulating blankets above and below the body Barbiturates were given to both groups at 6 to 8 mg/kg/h for the first 48 hours, then at 2 mg/kg/h for 3 days
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Hirayama 1994

Methods	Randomised controlled trial. Allocation method not stated.
Participants	Patients age 18 to 81, GCS 3-7 with closed head injury. Hypothermia started within 6 hours of injury
Interventions	Hypothermia patients: cooling to 32-33C for 48 hours using cooling blankets. Rewarming over a period of 48 hours. Control patients: Not stated.
Outcomes	Death and GOS at 3 months. ICP during treatment period.
Notes	Blinding of outcome assessment not stated.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Ishikura 1998

Methods	Randomised controlled trial. Allocation by 'random sampling'
Participants	Patients with GCS 3-8 with closed head injury.
Interventions	'Moderate hypothermia' without any details.
Outcomes	Thrombopoetin levels during treatment. Deaths in hypothermia arm only.
Notes	Abstract only.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	'11 patients with severe closed head injuries were divided into two groups by random sampling.' No information provided on allocation concealment

Jiang 2000

Methods	Randomised controlled trial. Allocation method not clear.
Participants	Patients with mean age of 41 years, GCS 3-8.
Interventions	Hypothermia patients: 'Mild hypothermia' induced using cooling blankets until ICP within 'normal range' for 24 hours. Control patients: Temperature maintained between 37-38C for 14 days
Outcomes	Death and GOS at 12 months. Complications.
Notes	Assessment by MD blinded to treatment allocation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Marion 1997

Methods	Randomised controlled trial. Allocation by 'sealed envelopes'
Participants	Patients age 16 to 75, GCS 3-7 with closed head injury, in whom cooling could begin within 6 hours of injury

Marion 1997 (*Continued*)

Interventions	Hypothermia patients: Cooling to 32-33C for 24 hours using cooling blankets and nasogastric lavage. Rewarming over a period of 12 hours. Control patients: Active management of temperature to 37-38.5C during five day treatment period
Outcomes	Death and GOS at 3, 6 and 12 months. ICP and CPP values during treatment phase. Complications for subset.
Notes	GOS assessment by psychiatrist blinded to treatment allocation

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	'Using a block-randomization scheme, we assigned patients with a Glasgow coma score of 3 or 4 to a treatment group separately from those with a score of 5 to 7 by choosing among equal numbers of sealed envelopes containing the group assignments.' p.540

Meissner 1998

Methods	Randomised controlled trial.
Participants	Patients with severe blunt head injury, in whom cooling could begin within 8 hours of injury
Interventions	Hypothermia patients: Cooling to 32-33C for 48 hours. Control patients: Temperature maintained at 36-37C.
Outcomes	Death. Infections.
Notes	GOS assessed at 6 months by non-blinded assessor, but not yet available

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	By 'sealed envelopes'.

Meissner 2003a

Methods	Randomised controlled trial.
Participants	Patients with severe blunt head injury. Intervention was started within 8 hours of injury
Interventions	Hypothermia patients: Cooling to 32-33C for 48 hours. Control patients: Temperature maintained at 36-37C.
Outcomes	Heart rate. Mean blood pressure. Plasma cortisol.
Notes	Primary outcome of study was moderate hypothermia on the cardiovascular and cortisol response in severe head injury No mortality data reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Meissner 2003b

Methods	Randomised controlled trial.
Participants	Patients aged 18 or older, with severe closed head injury with a GCS <=9. Intervention was started within 8 hours of injury
Interventions	Hypothermia patients: Cooling to 32-33C for 24-48 hours. Cooling was by water blankets and forced air. Control patients: Temperature maintained at 36-37C.
Outcomes	TSH TT4 FT4 TT3 FT3 RT3
Notes	This study examined thyroid hormone response in relation to therapeutic hypothermia

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Qiu 2007

Methods	Randomised, controlled, double-blind trial.
Participants	Patients 18-65 years old with traumatic brain injury with a Glasgow Coma Scale score of 8 or less
Interventions	Hypothermia patients: Cooling to 33-35C for 4 days after craniotomy, using a cooling blanket and cooling head cap with circulating water at 4C. 'Natural' rewarming. Normothermia patients: cooling not used.
Outcomes	Mortality. ICP. Serum superoxide dismutase level. Glasgow Outcome Scale at 1 year post-intervention.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	'Allocation and randomization was concealed so that the study investigators were not aware to which group the patient would be assigned, and the allocation sequence was protected until assignment.' p.230

Shiozaki 1993

Methods	Randomised controlled trial.
Participants	Patients age 10 or over, GCS 8 or less with head injury, who 'required continuous infusion of barbiturates to control intracranial hypertension'. p.363
Interventions	Hypothermia patients: cooling to 33.5-34.5C using water-circulating cooling blankets for a minimum of 48 hours and until ICP was below 20 mmHg for 24 hours. Rewarming over a period of 24 hours. Control patients: No active temperature management.
Outcomes	Death and GOS at 6 months. Pneumonia. Complications during treatment. ICP and CPP values during treatment period for hypothermic arm only
Notes	GOS assessed blind to treatment allocation.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Shiozaki 1999

Methods	Randomised controlled trial. Allocation concealment not clear. No loss to follow up.
Participants	Patients age 10 and above with traumatic brain injury, a Glasgow coma scale of 8 or less, and 'who required continuous infusion of barbiturate medication to control intracranial hypertension.' p.185
Interventions	Hypothermia patients: cooling to 33.5-34.5C for 48 hours, using water circulating blankets. Rewarming at 1C per day. Normothermia patients: maintained at 36.5-37.5C.
Outcomes	Death and GOS at 6 months. Complications.
Notes	Blinding of outcome assessment not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not described.

Shiozaki 2001

Methods	Randomised controlled trial. Allocation concealment not clear. No loss to follow up.
Participants	Patients with traumatic brain injury, a Glasgow coma scale of 8 or less, and 'in whom ICP was maintained below 25mmHg by conventional therapies'. p.50
Interventions	Hypothermia patients: Cooling to 33.5-34.5C for 48 hours, using cooling blankets and gastric lavage. Rewarming at 1C per day. Normothermia patients: maintained at 36.5-37.5C.
Outcomes	Death and GOS at 3 months. Complications
Notes	Blinding of outcome assessment not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not described.

Smrcka 2005

Methods	Randomised controlled trial - randomisation method not described. No loss to follow up described.
Participants	Patients with traumatic brain injury with a Glasgow Coma Scale score of 8 or less, who were up to age 61 years of age
Interventions	Hypothermia (n=37): surface cooling to 34C for 72 hours. Temperature measured in urinary bladder. Passive rewarming Normothermia (n=35): cooling not used.
Outcomes	ICP CPP $SvjO_2$ (jugular bulb oxygen saturation) GOS
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Yan 2001

Methods	Randomised controlled trial. Allocation concealment not described. No loss to follow up described.
Participants	Patients with traumatic brain injury within 10 hours of injury and a Glasgow Coma Scale of 3 to 8 on initial assessment
Interventions	Hypothermia patients: Cooling to 32-34C for 3-5 days, using a cooling bed and, in some, ice blocks. 'Natural' rewarming. Normothermia patients: cooling not used.
Outcomes	Death, follow up period unclear. Neuroelectrophysiological measurements.
Notes	Blinding of outcome assessment not stated.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

Zhang 2000

Methods	Randomised controlled trial. Allocation concealment not described. No loss to follow up mentioned
Participants	Patients aged under 65 with traumatic brain injury and a Glasgow Coma Scale of 3-8 on admission to hospital
Interventions	Hypothermia patients: Cooling to 32-33C for 3-8 days. Normothermia patients: temperature not stated.
Outcomes	Death, follow up period unclear.
Notes	Blinding of outcome assessment not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Not described.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chouhan 2006	Patients were not cooled for a minimum of 12 consecutive hours
Fukuoka 2004	Quasi-randomised study design.
Gentilello 1997	Randomised trial of rewarming therapy after accidental hypothermia in trauma
Hayashi 2002	Not a randomised study.
Hayashi 2005	Not a randomised study.
Legros 1985	Not a randomised study.
Liu 2005	Patients who died within 72 hours of participating in the study were not included in the analysis
Liu 2006	Patients were not cooled for a minimum of 12 consecutive hours
Nara 1997	Unable to find sufficient information on study design.
Nordby 1984	Not a randomised comparison, and hypothermia confounded with barbituate therapy
Schulman 2005	Patients to this study were excluded if they had evidence of acute brain injury and if they had previous traumatic brain injury

(*Continued*)

Shen 2000	Not a randomised trial.
Wusi 2006	Not a randomised trial.
Yamagami 1997	Not a randomised trial; hypothermia group GCS 4-6, normothermia group GCS 8-10

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chen 2001

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Guo 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Hutchison 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	Data to be included in this review for issue 2, 2009.

Mrlian 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Qiu 2005

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Qiu 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Wang 2005

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Wang 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Xia 2005

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Yan 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Zhi 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting clarification from authors about method of randomisation and allocation concealment

Characteristics of ongoing studies *[ordered by study ID]*

Adelson 2007

Trial name or title	Pediatric traumatic brain injury consortium: hypothermia.
Methods	Treatment, Randomized, Single Blind (outcome assessor), single group assignment, efficacy study
Participants	TBI patients under 16 years of age, with a GCS </= 8.
Interventions	Patients in the treatment arm will be cooled to 32-33C for 48 hours and then slowly rewarmed
Outcomes	• To determine the effect of induced moderate hypothermia (32-33C) after severe TBI in children on mortality. • To determine the effect of hypothermia after severe TBI in children on global function and neurocognitive outcomes in the areas of intellectual ability/development, memory and learning, and behaviour. • To determine the effect of hypothermia after severe TBI in children of different age ranges (<6y and 6 to <16y) on mortality and 6 and 12 months functional and neurocognitive outcomes. • To determine the effect of hypothermia after severe TBI in children on reducing intracranial hypertension and maintaining adequate cerebral perfusion pressure (CPP).
Starting date	November 2007
Contact information	P. David Adelson +1(412)692-6347 david.adelson@chp.edu S. Danielle Brown +1(412)692-8794 brownds2@upmc.edu
Notes	Phase III Clinical Trial.

Clifton 2002

Trial name or title	National Acute Brain Injury Study: Hypothermia II (NABISH II)
Methods	Randomized, prospective, multi-center trial. Hypothermia for 48 hours, begun within 6 hours of severe brain injury
Participants	Patients aged 16 to 45 years inclusive who have a closed head injury, present to the Emergency Department with a Glasgow Coma Score between 3-8, have a body temperature (bladder or rectal) of 35 degrees Celsius or less at admission, and an Abbreviated Injury Score (AIS) of 4 or less for the rest of the body
Interventions	The patients will be randomly allocated to either the hypothermia group or the normothermia group. A cooling suit will be used to cool the hypothermia patients down to a body temperature of 33 degrees Celsius. This temperature of 33 degrees will be maintained in the hypothermia patients for 48 hours. After 48 hours, the study nurses will gradually re-warm the hypothermia patients no faster than one degree every four hours. This takes at least 16 hours sometimes longer depending upon the stability of the patient's vital signs. The control group - normothermia will be allowed to re-warm gradually upon arrival to the hospital with no medical intervention to raise or lower the body temperature

Clifton 2002 (*Continued*)

Outcomes	Mortality and GOS. ICP and complications. Outcomes will be measured 6 months post injury by Harvey Levin, MD at Baylor College of Medicine. The personnel conducting outcome measurements will be blinded to the patient's assigned treatment protocol (whether hypothermia or normothermia)
Starting date	4/1/02 - 6/30/08
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Notes	There are other study sites participating in NABISH II. They are: University of Pittsburgh, Duke University, University of California at Los Angeles, University of California at Sacramento, University of California at San Francisco, University of Virginia at Fairfax, University of Cincinnati, University of Mississippi at Jackson