# Hypothermia for traumatic head injury (Review)

**Sydenham E, Roberts I, Alderson P**


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[Intervention Review]

# Hypothermia for traumatic head injury

Emma Sydenham[1], Ian Roberts[1], Phil Alderson[2]

[1]Cochrane Injuries Group, London School of Hygiene & Tropical Medicine, London, UK. [2]National Institute for Health and Clinical Excellence, Manchester, UK

Contact address: Emma Sydenham, Cochrane Injuries Group, London School of Hygiene & Tropical Medicine, Room 280, Keppel Street, London, WC1E 7HT, UK. emma.sydenham@lshtm.ac.uk. (Editorial group: Cochrane Injuries Group.)

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## 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, ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index-Science (CPCI-S), CENTRAL (*The Cochrane Library)*, MEDLINE and EMBASE. We handsearched conference proceedings and checked reference lists of all relevant articles. The search was last updated in January 2009.

### Selection criteria

Randomised controlled trials of hypothermia to a maximum of 35ºC for at least 12 consecutive 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 23 trials with a total of 1614 randomised patients. Twenty-one trials involving 1587 patients reported deaths. There were fewer deaths in patients treated with hypothermia than in the control group (OR 0.84, 95% CI 0.67 to 1.05). Nine trials with good allocation concealment showed no decrease in the likelihood of death compared with the control group, and this result was not statistically significant (OR 1.08, 95% CI 0.79 to 1.47). Twenty-one trials involving 1587 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 0.76, 95% CI 0.61 to 0.93). Nine trials with good allocation concealment showed patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group, but the reduction was small and non-

significant (OR 0.91, 95% CI 0.69 to 1.20). Hypothermia treatment was associated with a slight increase in the odds of pneumonia (OR 1.31, 95% CI 0.93 to 1.86) but there was a reduction in pneumonia for trials with good allocation concealment (4 trials analysed separately, 294 patients, OR 0.79, 95% CI 0.49 to 1.27) although in both cases the results are not statistically significant.

**Authors' conclusions**

There is no evidence that hypothermia is beneficial in the treatment of head injury. 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 no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant and could be due to the play of chance. Hypothermia should not be used except in the context of a high quality randomised controlled trial with good allocation concealment.

## PLAIN LANGUAGE SUMMARY

**Hypothermia (body temperature cooling) for traumatic head injury**

Twenty-three randomised controlled trials involving 1614 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 consecutive 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 were 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 somewhat effective in reducing death and disability among head injured patients. However, the good quality trials showed no decrease in the likelihood of death with hypothermia treatment and a reduced likelihood of pneumonia. Some of the findings in this review are therefore contradictory, and this is probably due to the inclusion of data from low quality trials.

The review authors conclude that there is no evidence that hypothermia is beneficial in the treatment of head injury. Most of the positive and negative effects found may be due to the play of chance. Hypothermia should not be used except in the context of a randomised controlled trial with good allocation concealment.

## 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 (Langlois 2006). 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 hy-

pothermia 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 possible 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 35ºC 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

The searches were not restricted by language, date or publication status.

### Electronic searches

We searched the following electronic databases:

- CENTRAL (*The Cochrane Library* Issue 4, 2008);
- MEDLINE (1950 to Jan 2009);
- PubMed: (searched 12 Jan 2009);
- EMBASE: (1980 to Jan 2009)
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to Jan 2009 and Conference Proceedings Citation Index-Science (CPCI-S) 1990 to Jan 2009;
- Zetoc.

The latest search strategies are listed in Appendix 1. The original search strategy from the first version of the review is in Appendix 2.

### Searching other resources

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, unpublished or ongoing trials.

## 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 23 randomised controlled trials were identified that met the inclusion criteria.

### Included studies

The 23 included randomised controlled trials involved 1614 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 eleven trials.

## Risk of bias in included studies

### Allocation

Adequate allocation concealment is an important dimension of trial quality.

Nine trials had a reasonable standard of allocation concealment (Adelson 2005 HYPO1; Adelson 2005 HYPO2; Clifton 1992; Clifton 1993; Clifton 2001; Hutchison 2008; 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-one trials involving 1587 patients reported deaths. Patients treated with hypothermia were somewhat less likely to die than those in the control group, but the reduction was not significant (OR 0.84, 95% CI 0.67 to 1.05). There was no evidence of statistical heterogeneity between trials ($Chi^2 = 20.61$, df = 19 (P = 0.36); $I^2 = 8\%$).

### Death at final follow-up stratified by trial quality

Analysis 1.2

Nine trials involving 891 patients used good allocation concealment methods. Hypothermia treatment was associated with no decrease in the likelihood of death, which was statistically non-significant compared with the control group (OR 1.08, 95% CI 0.79 to 1.47). There was no evidence of statistical heterogeneity between trials ($Chi^2 = 3.58$, df = 8 (P = 0.89); $I^2 = 0\%$).

Twelve trials involving 696 patients did not conceal allocation, or used 'unclear' concealment methods according to Higgins 2008. 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-one trials involving 1587 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 0.76, 95% CI 0.61 to 0.93). There was some evidence of statistical heterogeneity between trials ($Chi^2$ = 36.70, df = 20 (P = 0.01); $I^2$ = 45%).

### Unfavourable outcome stratified by trial quality

Analysis 1.4

Nine trials involving 891 patients used good allocation concealment methods. Hypothermia treatment was associated with a statistically non-significant small reduction in unfavourable outcome compared with the control group (OR 0.91, 95% CI 0.69 to 1.20). There was no statistical heterogeneity between trials ($Chi^2$ = 8.66, df = 8 (P = 0.37); $I^2$ = 8%).

Twelve trials involving 696 patients did not conceal allocation, or used 'unclear' concealment methods according to Higgins 2008. 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

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

Three trials involving 296 patients treated patients in the hypothermia group for 24 hours. There was a very slight, non-significant, reduction in the likelihood of unfavourable outcome for patients given hypothermia (OR 0.96, 95% CI 0.59 to 1.57). There was some statistical heterogeneity between trials ($Chi^2$ = 6.93, df = 2 (P = 0.03); $I^2$ = 71%).

Ten trials involving 683 patients treated patients in the hypothermia group for 48 hours. Hypothermia treatment was associated with a very slight, 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

Fifteen 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 unfavourable outcome 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%).

Nine trials involving 839 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, but the reduction was not significant (OR 0.76, 95% CI 0.57 to 1.01). There was significant statistical heterogeneity between trials ($Chi^2$ = 27.77, df = 8 (P = 0.0005); $I^2$ = 71%).

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

Eleven trials involving 547 patients reported pneumonia cases. Patients treated with hypothermia were somewhat more likely to have pneumonia than those in the control group, but the increase was not significant (OR 1.31, 95% confidence interval 0.93 to 1.86).

Pneumonia was stratified by trial quality:

Four trials with good allocation concealment involving 294 patients reported pneumonia cases. Hypothermia treatment was associated with a statistically non-significant decrease in pneumonia (OR 0.79, 95% confidence interval 0.49 to 1.27). There was no statistical heterogeneity between trials ($Chi^2$ = 0.97, df = 3 (P = 0.81); $I^2$ = 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

There is no evidence that hypothermia is beneficial in the treatment of head injury. 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 no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant. Some of the findings in this review are therefore contradictory, and this is probably due to the inclusion of data from low quality trials. Most of the positive and negative effects of hypothermia found may be due to the play of chance.

### 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.
In trials with good allocation concealment, patients receiving hypothermia were slightly more likely to die, but this may be due to the play of chance. There was a non-significant reduction in pneumonia 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.
A broader review by Polderman 2008 summarises the findings of some of the trials included in this review.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is no evidence that hypothermia is beneficial in the treatment of head injury. 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 no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant and could be due to the play of chance. Hypothermia should not be used except in the context of a high quality 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.

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## REFERENCES

### References to studies included in this review


**Adelson 2005 HYPO1** *{published data only}*

Adelson PD, Ragheb J, Muizelaar JP, Kanev P, Brockmeyer D, Beers S, et al.Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005;**56**(4):740–54. [DOI: 10.1227/01.NEU.0000156471.50726.26]

**Adelson 2005 HYPO2** *{published data only}*

Adelson PD, Ragheb J, Muizelaar JP, Kanev P, Brockmeyer D, Beers S, et al.Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005;**56**(4):740–54. [DOI: 10.1227/01.NEU.0000156471.50726.26]

**Aibiki 2000** *{published data only}*

Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. *Critical Care Medicine* 2000;**28** (12):3902–6.

**Biswas 2002** *{published data only}*

Biswas AK, Bruce DA, Sklar FH, Bokovoy JL, Sommerauer JF. Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension. *Critical Care Medicine* 2002;**30**(12):2742–51. [DOI: 10.1097/01.CCM.000038209.56308.9E]

**Clifton 1992** *{published and unpublished data}*

Clifton GL, Allen S, Berry J, Koch SM. Systemic hypothermia in treatment of brain injury. *Journal of Neurotrauma* 1992;**9**:S487–95.

**Clifton 1993** *{published data only}*

Clifton GL. Hypothermia and hyperbaric oxygen as treatment modalities for severe head injury. *New Horizons* 1995;**3**:474–8.

Clifton GL. Hypothermia in the management of patients with head injury. Abstracts of the 2nd International Neurotrauma Symposium. Glasgow, 1993; Vol. July 4–9.

Clifton GL. Systemic hypothermia in treatment of severe brain injury. *Journal of Neurosurgical Anesthesiology* 1995;**7**:152–6.

Clifton GL. Systemic hypothermia in treatment of severe brain injury: A review and update. *Journal of Neurotrauma* 1995;**12**:923–7.

* Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC. A phase II study of moderate hypothermia in severe brain injury. *Journal of Neurotrauma* 1993;**10**:263–73.

**Clifton 2001** *{published data only}*

Clifton GL. Hypothermia in Neurotrauma. Abstracts of the 3rd International Neurotrauma Symposium. Toronto, Canada, 1995: July 22-27.

* Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, et al.Lack of effect of induction of hypothermia after acute brain injury. *New England Journal of Medicine* 2001;**344**(8):556–63.

**Hashiguchi 2003** *{published data only}*

Hashiguchi N, Shiozaki T, Ogura H, Tanaka H, Koh T, Noborio M, et al.Mild hypothermia reduces expression of heat shock protein 60 in leukocytes from severely head-injured patients. *The Journal of Trauma Injury, Infection, and Critical Care* 2003;**55**:1054–60. [DOI: 10.1097/01.TA.0000033252.43742.8B]

**Hirayama 1994** *{published data only}*

Hayashi N, Hirayama T, Udagawa A, Daimon W, Ohata M. Systemic Management of Cerebral Edema Based on a New Concept in Severe Head Injury Patients. *Acta Neurochirurgica* 1994;**60**(supplement): 541–3.

Hayashi N, Shibuya T, Kinoshita K, Jo S, Azuhata T, Mera K, Tanjo K. The cerebral thermal dysregulation and hypothermia treatment in severe brain injury patients. Abstracts of the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury. Williamsburg USA, 1997:May 25-29.

* Hirayama T, Katayama Y, Kano T, Hayashi N, Tsubokawa T. Impact of Moderate Hypothermia on Therapies for Intracranial Pressure Control in Severe Traumatic Brain Injury. In: Nagai H, Ishii S, Maeda M editor(s). *Intracranial Pressure IX*. Tokyo: Springer-Verlag, 1994:233–6.

Hirayama T, Katayama Y, Maeda T, Kawamata T, Tsubokawa T. Effects of moderate hypothermia on the evolution of cerebral contusion. Abstracts of the 3rd International Neurotrauma Symposium. Toronto, Canada, 1995:July 22-27.

**Hutchison 2008** *{published data only}*

Hutchison J, Ward R, Lacroix J, Hebert P, Barnes M, et al.Hypothermia therapy after traumatic brain injury in children. *The New England Journal of Medicine* 2008;**358**:2447–56.

**Ishikura 1998** *{published data only}*

Ishikura H, Yamagami K, Akahori M, Shoji Y, Fukui H, Tanaka T. Changes in Blood Platelet Count and Serum Thrombopoetin (TPO) level under Moderate Hypothermic Therapy in Traumatic Severe Closed Head Injury. *Critical Care Medicine* 1998;**26**(Supplement 1): A82.

**Jiang 2000** *{published data only}*

* Jiang JY, Yu MK, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *Journal of Neurosurgery* 2000;**93**:546–9.

Jiang JY, Zhu C. The mild hypothermia significantly decreases mortality of severe traumatic brain injured patients. Abstracts of the International Conference on Recent Advances in Neurotraumatology, Riccione, Italy, Sept 8-11 1996. 1996.

**Marion 1997** *{published data only}*

Clark RSB, Kochanek PM, Obrist WD, Wong HR, Billiar TR, Wisniewski SR, Marion DW. Cerebrospinal fluid and plasma nitrite and nitrate concentrations after head injury in humans. *Critical Care Medicine* 1996;**24**:1243–51.

Darby JM, Marion DW, Peitzman A, Carlier P, Obrist WD. Pulmonary complications in brain-injured patients treated with hypothermia. *Anesthesiology* 1992;**77**:A295.

Marion DW, Carlier P. Moderate therapeutic hypothermia improves outcome following severe traumatic brain injury. Abstracts of the 3rd International Neurotrauma Symposium. Toronto, Canada, 1995: July 22-27.

Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *Journal of Neurosurgery* 1993; **79**:354–62.

Marion DW, Palmer AM, DeKosky ST, Kochanek PM, Carlier PM.

Effect of moderate hypothermia on neurochemical mediators of secondary brain injury. *Journal of Neurosurgery* 1995;**82**:344A.

Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. Abstracts of the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury. Williamsburg USA, 1997:May 25-29.

* Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. *New England Journal of Medicine* 1997;**336**:540–6.

Resnick DK, Marion DW, Darby JM. The effect of hypothermia on the incidence of delayed traumatic intracerebral hemorrhage. *Neurosurgery* 1994;**34**:252–6.

**Meissner 1998** ***{published and unpublished data}***

Meissner W, Fritz H, Dohrn B, Specht M, Reinhart K. Influence of Hypothermia on Cytokine Concentrations in Head Injured Patients. *Critical Care Medicine* 1998;**26**(Supplement 1):A82.

**Meissner 2003a** ***{published data only}***

Meissner W, Fritz H, Dohm B, Krapp C, Reinhart K. Hormonal and haemodynamic consequences of moderate hypothermia in head injured patients. *Neurosciences* 2003:102–3.

**Meissner 2003b** ***{published data only}***

Meissner W, Krapp C, Kauf E, Dohrn B, Reinhart K. Thyroid hormone response to moderate hypothermia in severe brain injury. *Intensive Care Medicine* 2003;**29**:44–8. [DOI: 10.1007/s00134-002-1556-3]

**Qiu 2007** ***{published data only}***

Qiu W, Zhang Y, Sheng H, Zhang J, Wang W, Liu W, et al.Effects of therapeutic mild hypothermia on patients with severe traumatic brain injury after craniotomy. *Journal of critical care* 2007;**22**:229–36.

**Shiozaki 1993** ***{published and unpublished data}***

Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *Journal of Neurosurgery* 1993;**79**:363–8.

**Shiozaki 1999** ***{published data only}***

Shiozaki T, Kato A, Taneda M, Hayakata T, Hashiguchi N, Tanaka H. Little benefit from mild hypothermia therapy for severely head injured patients with low intracranial pressure. *Journal of Neurosurgery* 1999;**91**:185–91.

**Shiozaki 2001** ***{published data only}***

Shiozaki T, Hayakata T, Taneda M, Nakajima Y, Hashiguchi N, Fujimi S, et al.A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. *Journal of Neurosurgery* 2001;**94**:50–4.

**Smrcka 2005** ***{published data only}***

Smrcka M, Vidlak M, Maca K, Smrcka V, Gal R. The influence of mild hypothermia on ICP, CPP and outcome in patients with primary and secondary brain injury. *Acta Neurochirurgica* 2005;**95** (Suppl):273–5.

**Yan 2001** ***{published data only}***

Yan Y, Tang W. Changes of evoked potentials and evaluation of mild hypothermia for treatment of severe brain injury. *Chinese Journal of Traumatology* 2001;**4**:8–13.

**Zhang 2000** ***{published data only}***

Zhang K, Wang JX. Comparative study on mild hypothermia in patients with severe head injury and the most severe head injury. *Inner Mongolia Medical Journal* 2000;**32**:4–6.

## References to studies excluded from this review

**Chouhan 2006** ***{published data only}***

Chouhan RS, Dash HH, Bithal PK, Chaturvedi A, Pandia MP, Radhakrishnan M, et al.Intraoperative mild hypothermia for brain protection during intracranial aneurysm surgery. *J Anaesth Clin Pharmacol* 2006;**22**(1):21–8.

**Fukuoka 2004** ***{published data only}***

Aibiki M. Personal communication with author. September 10, 2008.

* Fukuoka N, Aibiki M, Tsukamoto T, Seki K, Morita S. Biphasic concentration change during continuous midazolam administration in brain-injured patients undergoing therapeutic moderate hypothermia. *Resuscitation* 2004;**60**:225–30.

**Gal 2002** ***{published data only}***

Gal R, Cundrle I, Zimova I, Smrcka M. Mild hypothermia therapy for patients with severe brain injury. *Clinical Neurology and Neurosurgery* 2002;**104**:318–21.

**Gentilello 1997** ***{published data only}***

Gentilello LM, Jurkovich GJ, Stark MS, Hassantash SA, O'Keefe GE. Is hypothermia in the victim of major trauma protective or harmful?. *Annals of Surgery* 1997;**226**:439–49.

**Hayashi 2002** ***{published data only}***

Hayashi S, Inao S, Takayasu M, Kajita Y, Ishiyama J, et al.Effect of early induction of hypothermia on severe head injury (abstract). *Acta Neurochirurgica* 2002;**81**(Suppl):83–4. [PUBMED: 12168365]

**Hayashi 2005** ***{published data only}***

Hayashi S, Takayasu M, Inao S, Yoshida J. Balance of risk of therapeutic hypothermia. *Acta Neurochirurgica* 2005;**95**(Suppl):269–72.

**Legros 1985** ***{published data only}***

Legros B, Lapierre F, Laudat P, Krettly PH, Fournier P, Meny J, et al.Barbiturate hypothermia treatment for post-traumatic brain injury:infectious complications and mortality [Barbiturici–ipotermia nella protezione metabolica cerebrale post–traumatica: complicazioni infettive e mortalita]. *Minerva Anesthesiologica* 1985;**51**:525–30.

**Liu 2005** ***{published data only}***

Liu W, An Y-H, Liu E-Z, Yu C-J. Effect of mild hypothermia combined with hibernation on the homeostasis of patients with severe head injury. *Chinese Journal of Clinical Rehabilitation* 2005;**9**(33): 175–7.

**Liu 2006** ***{published data only}***

Liu WG, Qiu WS, Zhang Y, Wang WM, Lu F, Yang XF. Effects of selective brain cooling in patients with severe traumatic brain injury: a preliminary study. *The Journal of International Medical Research* 2006;**34**:58–64.

**Nara 1997** *{published data only}*

Nara I, Shiogai T, Saruta K, Hara M, Saito I. Comparative effects of hypothermia, barbiturates, and osmotherapy for cerebral oxygen metabolism, intracranial pressure and cerebral perfusion pressure in patients with severe head injury. Abstracts of the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury. Williamsburg USA, 1997:May 25-29.

**Nordby 1984** *{published data only}*

Nordby HK, Nesbakken R. The effect of high-dose barbiturate compression after severe head Injury: a controlled clinical trial. *Acta Neurochirurgica* 1984;**72**:157–66.

**Schulman 2005** *{published data only}*

Schulman C, Namias N, Doherty J, Manning R, Li P, Alhaddad A, et al.The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surgical interventions* 2005;**6**(4):369–75.

**Shen 2000** *{published data only}*

Shen JH, Shen MW. Application of mild hypothermia in treatment of severe brain injury. *Heibei Med J* 2000;**6**:498–500.

**Wusi 2006** *{published data only}*

Wusi Q, Hong S, Ying Z, Weimin W, Weiguo L, Qizhou J, et al.Noninvasive selective brain cooling by head and neck cooling is protective in severe traumatic brain injury. *Journal of Clinical Neuroscience* 2006;**13**:995–1000.

**Yamagami 1997** *{published data only}*

Yamagami K, Iwase M, Matsubara M, Matsuo N, Tanaka T. Nitric oxide production and arginine consumption in traumatic brain injury are correlated with severity. Abstracts of the 26th Meeting of the Society for Critical Care Medicine. Critical Care Medicine. 1997; Vol. 25, issue supplement 1:A72.

## References to studies awaiting assessment

**Chen 2001** *{published data only}*

Chen L, Piao Y, Zeng F, Lu M, Kuang Y, Li X. Moderate hypothermia therapy for patients with severe head injury. *Chinese Journal of Traumatology (English edition)* 2001;**4**(3):164–7.

**Guo 2004** *{published data only}*

Guo W, Wang L-L, Cai K-H. A control study on mild hypothermia in treatment of severe craniocerebral injury. *Journal of Xinxiang Medical College* 2004;**21**(4):269–71.

**Mrlian 2006** *{published data only}*

Mrlian A, Smrcka M, Klabusay M. The use of controlled mild hypothermia and immune system status in patients with severe brain injury. *Bratisl Lek Listy* 2006;**107**(4):113–7.

**Qiu 2005** *{published data only}*

Qiu WS, Liu WG, Shen H, Wang WM, Zhang SL, Zhang Y, et al.Therapeutic effect of mild hypothermia on severe traumatic head injury. *Chinese Journal of Traumatology* 2005;**8**(1):27–32.

**Qiu 2006** *{published data only}*

Qiu W, Wang W, Du H, Liu W, Shen H, Shen L, et al.Thrombocytopenia after therapeutic hypothermia in severe traumatic brain injury. *Chinese Journal of Traumatology* 2006;**9**(4):238–41.

**Wang 2005** *{published data only}*

Wang WP, Ren HJ, Chi JY, Xu FL, Quan Y. Effects of mild hypothermia on patients with lower intracranial pressure following severe brain injury. *Chinese Journal of Traumatology* 2005;**8**(1):54–6.

**Wang 2007** *{published data only}*

Wang Q, Li AL, Zhi DS, Huang HL. Effect of mild hypothermia on glucose metabolism and glycerol of brain tissue in patients with severe traumatic brain injury. *Chinese Journal of Traumatology* 2007; **10**(4):246–9.

**Xia 2005** *{published data only}*

Xia YQ, Yan LL, Xu RX, Wang QH. Evaluation of improvement of subhypothermia in cerebral vasospasm after severe craniocerebral injury. *Chinese Journal of Clinical Rehabilitation* 2005;**9**(41):138–41.

**Yan 2007** *{published data only}*

Yan Y, Tang W, He J, Gao J, Dan W, Zhong D, et al.Clinical research about brain oxygen metabolism and neuroelectrophysiology during mild hypothermia in patients with severe head injury. *Chinese Journal of Surgery* 2007;**45**(2):109–13.

**Zhi 2003** *{published data only}*

Zhi D, Zhang S, Lin X. Study on the therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surgical Neurology* 2003;**59**:381–5. [DOI: 10.1016/S0090-3019(03)00148-4]

## References to ongoing studies

**Adelson 2007** *{unpublished data only}*

Pediatric traumatic brain injury consortium: hypothermia.. Ongoing study November 2007.

**Clifton 2002** *{unpublished data only}*

National Acute Brain Injury Study: Hypothermia II (NABISH II). Ongoing study 4/1/02 – 6/30/08.

## Additional references

**Adelson 2008a**

Adelson D. [Personal communication with author]. 5 October 2008.

**Adelson 2008b**

Adelson D. [Personal communication with author]. 17 October 2008.

**Alexander 1992**

Alexander E Jr. Global Spine and Head Injury Prevention Project (SHIP). *Surgical Neurology* 1992;**38**:478–9.

**Bering 1961**

Bering EA Jr. Effect of body temperature change on cerebral oxygen consumption of the intact monkey. *American Journal of Physiology* 1961;**200**:417–9.

**Bullock 1996**

Bullock R, Chesnut RM, Clifton G, Ghajar J, Marion DW, Narayan RK, et al.Guidelines for the management of severe head injury. *Journal of Neurotrauma* 1996;**13**:639–734.

**Busto 1987**

Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intra-ischemic brain temperature critically

determine the extent of ischemic neuronal injury. *Journal of Cerebral Blood Flow Metabolism* 1987;**7**:729–38.

**Busto 1989**

Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neuro-transmitters and free fatty acids in rat brain. *Stroke* 1989; **20**:904–10.

**Clasen 1968**

Clasen RA, Pandolfi S, Russell J, Stuart D, Hass GM. Hypothermia and hypotension in experimental cerebral edema. *Archives of Neurology* 1968;**19**:472–86.

**Clifton 1995**

Clifton GL. Systemic Hypothermia in Treatment of Severe Brain Injury : A Review and Update 1995. *Journal of Neurotrauma* 1995; **12**:923–7.

**Fay 1945**

Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. *Assoc Res Nerv Ment Dis Proc* 1945;**24**:611–9.

**Higgins 2008**

Higgins JPT, Green S (editors). The Cochrane Handbook of Systematic Reviews. The Cochrane Collaboration 2008; Vol. Version 5.0.0 [updated February 2008]:Available from www.cochrane-handbook.org.

**Kirkpatrick 1997**

Kirkpatrick PJ. On guidelines for the management of severe head injury. *Journal of Neurology, Neurosurgery and Psychiatry* 1997;**62**: 109–11.

**Langlois 2006**

Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of Head Trauma Rehabilitation* 2006;**21**(5):375–8.

**Laskowski 1960**

Laskowski EJ, Klato I, Baldwin M. Experimental study on the effects of hypothermia on local brain injury. *Neurology* 1960;**10**:499–505.

**Peterson 2008**

Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. *Journal of Neurotrauma* 2008;**25**:62–71. [DOI: 10.1089/neu.2007.0424]

**Polderman 2008**

Polderman K H. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008;**371**:1955–69.

**Review Manager (RevMan)**

The Nordic Cochrane Center. Review Manager (RevMan). 5.0.0. Copenhagen: The Cochrane Collaboration, 2008.

**Schubert 1995**

Schubert A. Side effects of mild hypothermia. *Journal of Neurosurgical Anesthesiology* 1995;**7**:139–47.

**Sedzimir 1959**

Sedzimir CB. Therapeutic hypothermia in cases of head injury. *Journal of Neurosurgery* 1959;**16**:407–14.

**Shapiro 1974**

Shapiro HM, Wyte SR, Loeser J. Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension. *Journal of Neurosurgery* 1974;**40**:90–100.

**Smith 1996**

Smith SL, Hall ED. Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage following controlled cortical impact injury in the rat. *Journal of Neurotrauma* 1996;**13**:1–9.

* *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.<br>Normothermia patients: no intervention/not reported. |
| Outcomes | ICP<br>CPP<br>Mortality<br>Infection<br>Arrhythmia<br>Coagulopathy<br>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.<br>Normothermia patients: no intervention/not reported. |
| Outcomes | ICP<br>CPP<br>Mortality<br>Infection<br>Arrhythmia |

**Adelson 2005 HYPO2** (*Continued*)

| | |
|---|---|
| | Coagulopathy<br>Pneumonia |
| 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.<br>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.<br>Normothermia patients: maintained at 36-37C. |
| Outcomes | Death and GOS at 6 months.<br>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.<br>Control patients (n=11): rectal temperature was maintained between 36.5 and 37.5 degrees Celsius. |
| Outcomes | Death.<br>GOS at three, six and 12 months.<br>ICP and CPP. |
| Notes | GOS assessed blind to allocation.<br>Analysis on an intention-to-treat basis.<br>Two patients in the hypo group were lost to follow-up and the end of the study period. (2/10 lost to follow-up.)<br>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.<br>Control patients: No active temperature management. |
| Outcomes | Death and GOS at 3 months.<br>Complications during treatment phase. |
| Notes | GOS was not assessed blind to treatment allocation. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Clifton 1992** (*Continued*)

| | | |
|---|---|---|
| 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. |
| Interventions | Hypothermia patients: cooling to 32-33C for 48 hours using cooling blankets. Rewarming over a period of 48 hours.<br>Control patients: Cooling blankets were used to maintain body temperature at 37C for 80 hours. |
| Outcomes | Death and GOS at 3 months.<br>Complications during treatment period.<br>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.<br>Control: Body temperature maintained at 37C. |
| Outcomes | Death and GOS at 6 months.<br>ICP monitored during treatment.<br>Nine neurobehavioural and neuropsychological scales at 6 months. |
| Notes | GOS was assessed blind to treatment allocation.<br>Outcome data missing for 7 patients, and not presented for 17 patients whose entry details were incomplete. |

**Clifton 2001** (*Continued*)

| *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". p557 |

**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.<br>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.<br>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.<br>Control patients: Not stated. |

**Hirayama 1994** (*Continued*)

| | |
|---|---|
| Outcomes | Death and GOS at 3 months.<br>ICP during treatment period. |
| Notes | Blinding of outcome assessment not stated. |

***Risk of bias***

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

**Hutchison 2008**

| | |
|---|---|
| Methods | Randomised controlled trial. |
| Participants | Patients age 1-17 years, with a recent traumatic brain injury (within 8 hours) and a GCS score of 8 or less. |
| Interventions | Hypothermia patients: cooling to 32-33C for 24 hours with surface cooling. Rewarming at a rate of 0.5C every 2 hours.<br>Control patients: temperature was maintained at 36.5 to 37.5C. |
| Outcomes | Unfavourable outcome at 6 months post-injury.<br>Pediatric Cerebral Performance Category scale at pre-injury, and at 1, 3 and 12 months post-injury. |
| Notes | 'Overall, 20 out of the 225 patients (9%) were lost to follow-up at 6 months -- 6 out of 108 patients (6%) in the hypothermia group and 14 of 117 (12%) in the normothermia group.' p.2451 |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | '...a study physician randomly assigned the patient to a treatment group with the use of a central telephone-based system that was available 24 hours a day. The randomization, prepared by an independent statistician, was blocked in groups of four (participating centers were unaware of the block size) and included two stratification variables: center and age (less than 7 years of age and 7 years of age or more).' p.2448 |

**Ishikura 1998**

| | |
|---|---|
| Methods | Randomised controlled trial. Allocation by 'random sampling'. |
| Participants | Patients with GCS 3-8 with closed head injury. |

**Ishikura 1998** (*Continued*)

| | |
|---|---|
| Interventions | 'Moderate hypothermia' without any details. |
| Outcomes | Thrombopoetin levels during treatment.<br>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.<br>Control patients: Temperature maintained between 37-38C for 14 days. |
| Outcomes | Death and GOS at 12 months.<br>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.<br>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.<br>ICP and CPP values during treatment phase.<br>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.<br>Control patients: Temperature maintained at 36-37C. |
| Outcomes | Death.<br>Infections. |
| Notes | GOS assessed at 6 months by non-blinded assessor. |

***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.<br>Control patients: Temperature maintained at 36-37C. |
| Outcomes | Heart rate.<br>Mean blood pressure.<br>Plasma cortisol. |
| Notes | Primary outcome of study was moderate hypothermia on the cardiovascular and cortisol response in severe head injury.<br>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.<br>Control patients: Temperature maintained at 36-37C. |
| Outcomes | TSH<br>TT4<br>FT4<br>TT3<br>FT3<br>RT3 |
| Notes | This study examined thyroid hormone response in relation to therapeutic hypothermia. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

**Meissner 2003b** (*Continued*)

| | | |
|---|---|---|
| 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.<br>Normothermia patients: cooling not used. |
| Outcomes | Mortality.<br>ICP.<br>Serum superoxide dismutase level.<br>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.<br>Control patients: No active temperature management. |
| Outcomes | Death and GOS at 6 months.<br>Pneumonia.<br>Complications during treatment.<br>ICP and CPP values during treatment period for hypothermic arm only. |
| Notes | GOS assessed blind to treatment allocation. |

**Shiozaki 1993** (*Continued*)

| ***Risk of bias*** | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | Not described. |

**Shiozaki 1999**

| | |
|---|---|
| Methods | Randomised controlled trial. Allocation concealment not clear.<br>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.<br>Normothermia patients: maintained at 36.5-37.5C. |
| Outcomes | Death and GOS at 6 months.<br>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.<br>Allocation concealment not clear.<br>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.<br>Normothermia patients: maintained at 36.5-37.5C. |

**Shiozaki 2001** (*Continued*)

| | |
|---|---|
| Outcomes | Death and GOS at 3 months.<br>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.<br>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.<br>Normothermia (n=35): cooling not used. |
| Outcomes | ICP<br>CPP<br>$SvjO_2$ (jugular bulb oxygen saturation)<br>GOS |
| Notes | |

***Risk of bias***

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

**Yan 2001**

| | |
|---|---|
| Methods | Randomised controlled trial.<br>Allocation concealment not described.<br>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. |

**Yan 2001** (*Continued*)

| | |
|---|---|
| Interventions | Hypothermia patients: Cooling to 32-34C for 3-5 days, using a cooling bed and, in some, ice blocks. 'Natural' rewarming.<br>Normothermia patients: cooling not used. |
| Outcomes | Death, follow up period unclear.<br>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.<br>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.<br>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]*

| | |
|---|---|
| Chouhan 2006 | Patients were not cooled for a minimum of 12 consecutive hours. |
| Fukuoka 2004 | Quasi-randomised study design. |
| Gal 2002 | Not a randomised study. |
| 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 barbiturate therapy. |
| Schulman 2005 | Patients in this study were excluded if they had evidence of acute brain injury and if they had previous traumatic brain injury. |
| 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 | |

**Chen 2001** (*Continued*)

| | |
|---|---|
| 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. |

**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 | |

**Xia 2005** (*Continued*)

| | |
|---|---|
| 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. |

**Adelson 2007** (*Continued*)

| | |
|---|---|
| | • 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.<br>• 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.<br>• 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<br>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. |
| Outcomes | Mortality and GOS. ICP and complications.<br>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 |
| Contact information | Guy L. Clifton, MD<br>Chairman Neurosurgery Dept., University of Texas Medical School<br>6431 Fannin St., Suite 7.148<br>Houston, TX 77030 |

**Clifton 2002** (*Continued*)

| | |
|---|---|
| | 713-500-6135<br>guy.l.clifton@uth.tmc.edu<br>Emmy R. Miller, RN, PhD, Co-investigator NABISH II<br>Associate Professor of Neurosurgery<br>University of Texas Medical School, Houston, TX<br>6431 Fannin St., Suite 7.148<br>Houston, TX 77030<br>713-500-6145<br>Emmy.R.Miller@uth.tmc.edu |
| Notes | There are other study sites participating in NABISH II.<br>They are:<br>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. |

## DATA AND ANALYSES

### Comparison 1. Immediate hypothermia versus normothermia

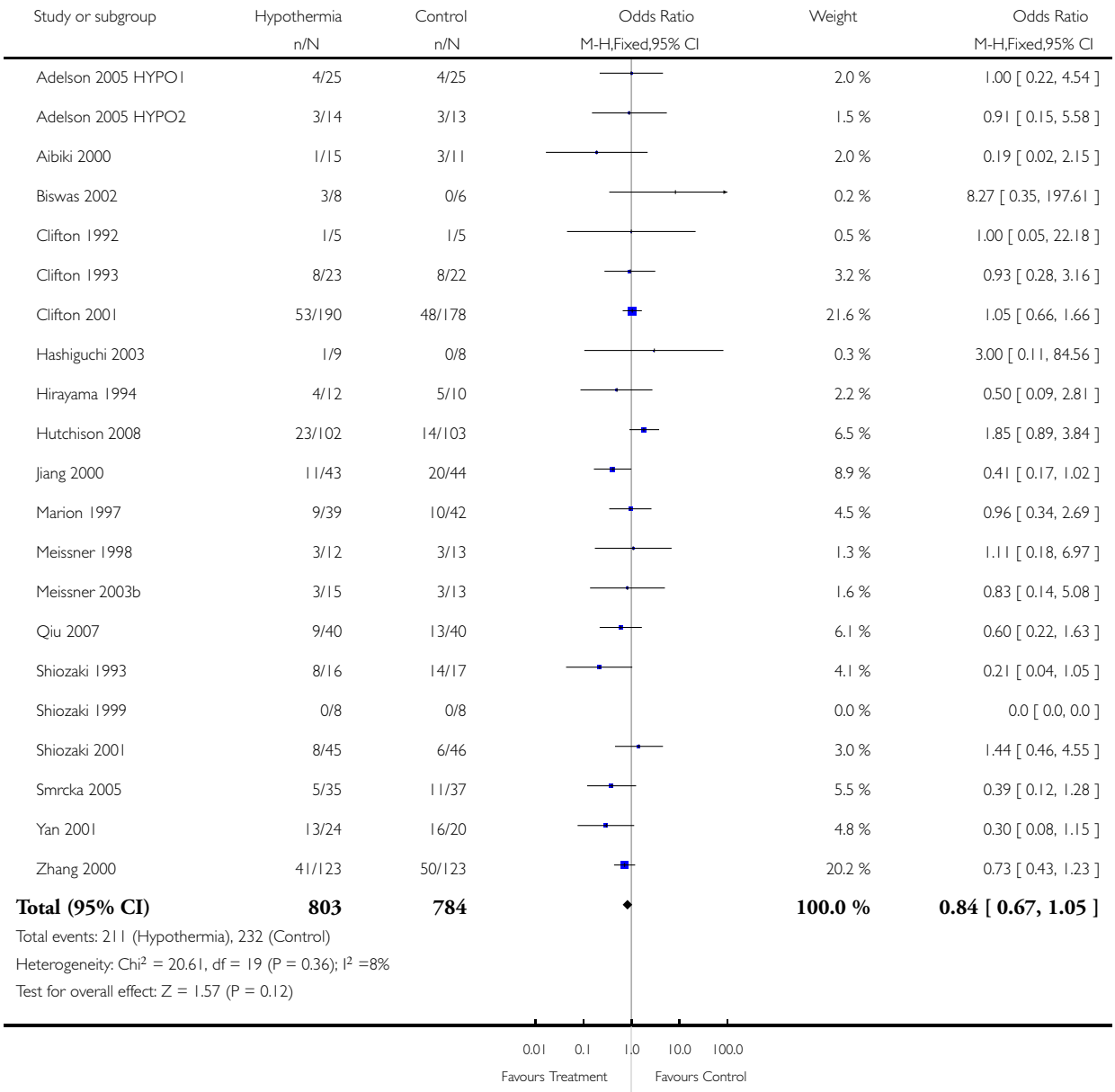
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Death at final follow-up | 21 | 1587 | Odds Ratio (M-H, Fixed, 95% CI) | 0.84 [0.67, 1.05] |
| 2 Death at final follow-up stratified by trial quality | 21 | 1587 | Odds Ratio (M-H, Fixed, 95% CI) | 0.84 [0.67, 1.05] |
| 2.1 Concealed allocation | 9 | 891 | Odds Ratio (M-H, Fixed, 95% CI) | 1.08 [0.79, 1.47] |
| 2.2 Non-concealed allocation | 12 | 696 | Odds Ratio (M-H, Fixed, 95% CI) | 0.62 [0.44, 0.86] |
| 3 Unfavourable outcome at final follow-up | 21 | 1587 | Odds Ratio (M-H, Fixed, 95% CI) | 0.76 [0.61, 0.93] |
| 4 Unfavourable outcome stratified by trial quality | 21 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.1 Concealed allocation | 9 | 891 | Odds Ratio (M-H, Fixed, 95% CI) | 0.91 [0.69, 1.20] |
| 4.2 Non-concealed allocation | 12 | 696 | Odds Ratio (M-H, Fixed, 95% CI) | 0.60 [0.44, 0.82] |
| 5 Unfavourable outcome stratified by treatment duration | 13 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.1 24 hours | 3 | 296 | Odds Ratio (M-H, Fixed, 95% CI) | 0.96 [0.59, 1.57] |
| 5.2 48 hours | 10 | 683 | Odds Ratio (M-H, Fixed, 95% CI) | 0.96 [0.70, 1.31] |
| 6 Unfavourable outcome at various times during follow-up | 15 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 6.1 3 months | 6 | 271 | Odds Ratio (M-H, Fixed, 95% CI) | 0.85 [0.52, 1.39] |
| 6.2 6 months | 9 | 839 | Odds Ratio (M-H, Fixed, 95% CI) | 0.76 [0.57, 1.01] |
| 6.3 12 months | 4 | 262 | Odds Ratio (M-H, Fixed, 95% CI) | 0.52 [0.31, 0.87] |
| 7 Pneumonia during the treatment period | 11 | 547 | Odds Ratio (M-H, Fixed, 95% CI) | 1.31 [0.93, 1.86] |
| 7.1 Concealed allocation | 4 | 294 | Odds Ratio (M-H, Fixed, 95% CI) | 0.79 [0.49, 1.27] |
| 7.2 Non-concealed allocation | 7 | 253 | Odds Ratio (M-H, Fixed, 95% CI) | 2.47 [1.44, 4.23] |

## Analysis 1.1. Comparison 1 Immediate hypothermia versus normothermia, Outcome 1 Death at final follow-up.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 1 Death at final follow-up



## Analysis 1.2. Comparison 1 Immediate hypothermia versus normothermia, Outcome 2 Death at final follow-up stratified by trial quality.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 2 Death at final follow-up stratified by trial quality

| Study or subgroup | Experimental n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Concealed allocation | | | | | |
| Adelson 2005 HYPO1 | 4/25 | 4/25 | | 2.0 % | 1.00 [ 0.22, 4.54 ] |
| Adelson 2005 HYPO2 | 3/14 | 3/13 | | 1.5 % | 0.91 [ 0.15, 5.58 ] |
| Clifton 1992 | 1/5 | 1/5 | | 0.5 % | 1.00 [ 0.05, 22.18 ] |
| Clifton 1993 | 8/23 | 8/22 | | 3.2 % | 0.93 [ 0.28, 3.16 ] |
| Clifton 2001 | 53/190 | 48/178 | | 21.6 % | 1.05 [ 0.66, 1.66 ] |
| Hutchison 2008 | 23/102 | 14/103 | | 6.5 % | 1.85 [ 0.89, 3.84 ] |
| Marion 1997 | 9/39 | 10/42 | | 4.5 % | 0.96 [ 0.34, 2.69 ] |
| Meissner 1998 | 3/12 | 3/13 | | 1.3 % | 1.11 [ 0.18, 6.97 ] |
| Qiu 2007 | 9/40 | 13/40 | | 6.1 % | 0.60 [ 0.22, 1.63 ] |
| **Subtotal (95% CI)** | **450** | **441** | | **47.3 %** | **1.08 [ 0.79, 1.47 ]** |
| Total events: 113 (Experimental), 104 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.58, df = 8 (P = 0.89); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.49 (P = 0.62) | | | | | |
| 2 Non-concealed allocation | | | | | |
| Aibiki 2000 | 1/15 | 3/11 | | 2.0 % | 0.19 [ 0.02, 2.15 ] |
| Biswas 2002 | 3/8 | 0/6 | | 0.2 % | 8.27 [ 0.35, 197.61 ] |
| Hashiguchi 2003 | 1/9 | 0/8 | | 0.3 % | 3.00 [ 0.11, 84.56 ] |
| Hirayama 1994 | 4/12 | 5/10 | | 2.2 % | 0.50 [ 0.09, 2.81 ] |
| Jiang 2000 | 11/43 | 20/44 | | 8.9 % | 0.41 [ 0.17, 1.02 ] |
| Meissner 2003b | 3/15 | 3/13 | | 1.6 % | 0.83 [ 0.14, 5.08 ] |
| Shiozaki 1993 | 8/16 | 14/17 | | 4.1 % | 0.21 [ 0.04, 1.05 ] |
| Shiozaki 1999 | 0/8 | 0/8 | | 0.0 % | 0.0 [ 0.0, 0.0 ] |
| Shiozaki 2001 | 8/45 | 6/46 | | 3.0 % | 1.44 [ 0.46, 4.55 ] |
| Smrcka 2005 | 5/35 | 11/37 | | 5.5 % | 0.39 [ 0.12, 1.28 ] |
| Yan 2001 | 13/24 | 16/20 | | 4.8 % | 0.30 [ 0.08, 1.15 ] |
| Zhang 2000 | 41/123 | 50/123 | | 20.2 % | 0.73 [ 0.43, 1.23 ] |


(*Continued . . .*)

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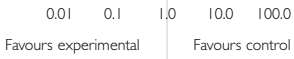
| Study or subgroup | Experimental n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **353** | **343** | | **52.7 %** | **0.62 [ 0.44, 0.86 ]** |
| Total events: 98 (Experimental), 128 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 11.14, df = 10 (P = 0.35); $I^2$ =10% | | | | | |
| Test for overall effect: Z = 2.83 (P = 0.0046) | | | | | |
| **Total (95% CI)** | **803** | **784** | | **100.0 %** | **0.84 [ 0.67, 1.05 ]** |
| Total events: 211 (Experimental), 232 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 20.61, df = 19 (P = 0.36); $I^2$ =8% | | | | | |
| Test for overall effect: Z = 1.57 (P = 0.12) | | | | | |




Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

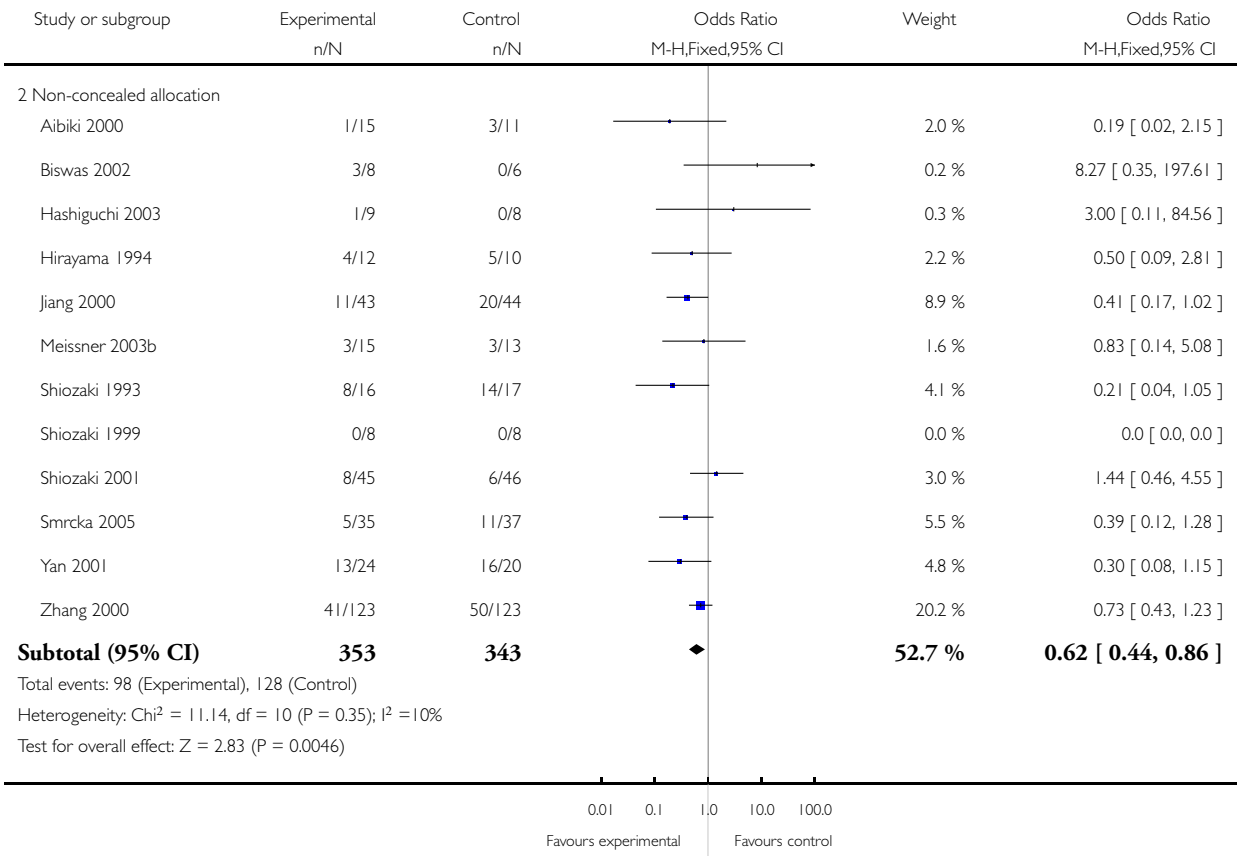
Outcome: 2 Death at final follow-up stratified by trial quality

| Study or subgroup | Experimental n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Concealed allocation | | | | | |
| Adelson 2005 HYPO1 | 4/25 | 4/25 | | 2.0 % | 1.00 [ 0.22, 4.54 ] |
| Adelson 2005 HYPO2 | 3/14 | 3/13 | | 1.5 % | 0.91 [ 0.15, 5.58 ] |
| Clifton 1992 | 1/5 | 1/5 | | 0.5 % | 1.00 [ 0.05, 22.18 ] |
| Clifton 1993 | 8/23 | 8/22 | | 3.2 % | 0.93 [ 0.28, 3.16 ] |
| Clifton 2001 | 53/190 | 48/178 | | 21.6 % | 1.05 [ 0.66, 1.66 ] |
| Hutchison 2008 | 23/102 | 14/103 | | 6.5 % | 1.85 [ 0.89, 3.84 ] |
| Marion 1997 | 9/39 | 10/42 | | 4.5 % | 0.96 [ 0.34, 2.69 ] |
| Meissner 1998 | 3/12 | 3/13 | | 1.3 % | 1.11 [ 0.18, 6.97 ] |
| Qiu 2007 | 9/40 | 13/40 | | 6.1 % | 0.60 [ 0.22, 1.63 ] |
| **Subtotal (95% CI)** | **450** | **441** | | **47.3 %** | **1.08 [ 0.79, 1.47 ]** |
| Total events: 113 (Experimental), 104 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.58, df = 8 (P = 0.89); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.49 (P = 0.62) | | | | | |

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 2 Death at final follow-up stratified by trial quality



### Analysis 1.3. Comparison 1 Immediate hypothermia versus normothermia, Outcome 3 Unfavourable outcome at final follow-up.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 3 Unfavourable outcome at final follow-up

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Adelson 2005 HYPO1 | 4/25 | 4/25 | | 1.6 % | 1.00 [ 0.22, 4.54 ] |
| Adelson 2005 HYPO2 | 3/14 | 3/13 | | 1.2 % | 0.91 [ 0.15, 5.58 ] |
| Aibiki 2000 | 3/15 | 7/11 | | 3.1 % | 0.14 [ 0.02, 0.83 ] |
| Biswas 2002 | 3/8 | 0/6 | | 0.2 % | 8.27 [ 0.35, 197.61 ] |
| Clifton 1992 | 1/5 | 2/5 | | 0.8 % | 0.38 [ 0.02, 6.35 ] |
| Clifton 1993 | 11/23 | 14/22 | | 3.6 % | 0.52 [ 0.16, 1.73 ] |
| Clifton 2001 | 108/190 | 102/178 | | 22.1 % | 0.98 [ 0.65, 1.48 ] |
| Hashiguchi 2003 | 3/9 | 1/8 | | 0.3 % | 3.50 [ 0.28, 43.16 ] |
| Hirayama 1994 | 4/12 | 7/10 | | 2.5 % | 0.21 [ 0.04, 1.31 ] |
| Hutchison 2008 | 32/102 | 23/103 | | 7.6 % | 1.59 [ 0.85, 2.97 ] |
| Jiang 2000 | 23/43 | 32/44 | | 7.1 % | 0.43 [ 0.18, 1.05 ] |
| Marion 1997 | 15/39 | 26/42 | | 7.5 % | 0.38 [ 0.16, 0.94 ] |
| Meissner 1998 | 3/12 | 3/13 | | 1.0 % | 1.11 [ 0.18, 6.97 ] |
| Meissner 2003b | 3/15 | 3/13 | | 1.2 % | 0.83 [ 0.14, 5.08 ] |
| Qiu 2007 | 9/40 | 13/40 | | 4.9 % | 0.60 [ 0.22, 1.63 ] |
| Shiozaki 1993 | 10/16 | 16/17 | | 2.8 % | 0.10 [ 0.01, 1.00 ] |
| Shiozaki 1999 | 2/8 | 1/8 | | 0.4 % | 2.33 [ 0.17, 32.58 ] |
| Shiozaki 2001 | 24/45 | 19/46 | | 4.3 % | 1.62 [ 0.71, 3.72 ] |
| Smrcka 2005 | 5/35 | 19/37 | | 7.7 % | 0.16 [ 0.05, 0.50 ] |
| Yan 2001 | 13/24 | 16/20 | | 3.9 % | 0.30 [ 0.08, 1.15 ] |
| Zhang 2000 | 41/123 | 50/123 | | 16.2 % | 0.73 [ 0.43, 1.23 ] |
| **Total (95% CI)** | **803** | **784** | | **100.0 %** | **0.76 [ 0.61, 0.93 ]** |

Total events: 320 (Hypothermia), 361 (Control)

Heterogeneity: $Chi^2$ = 36.70, df = 20 (P = 0.01); $I^2$ =45%

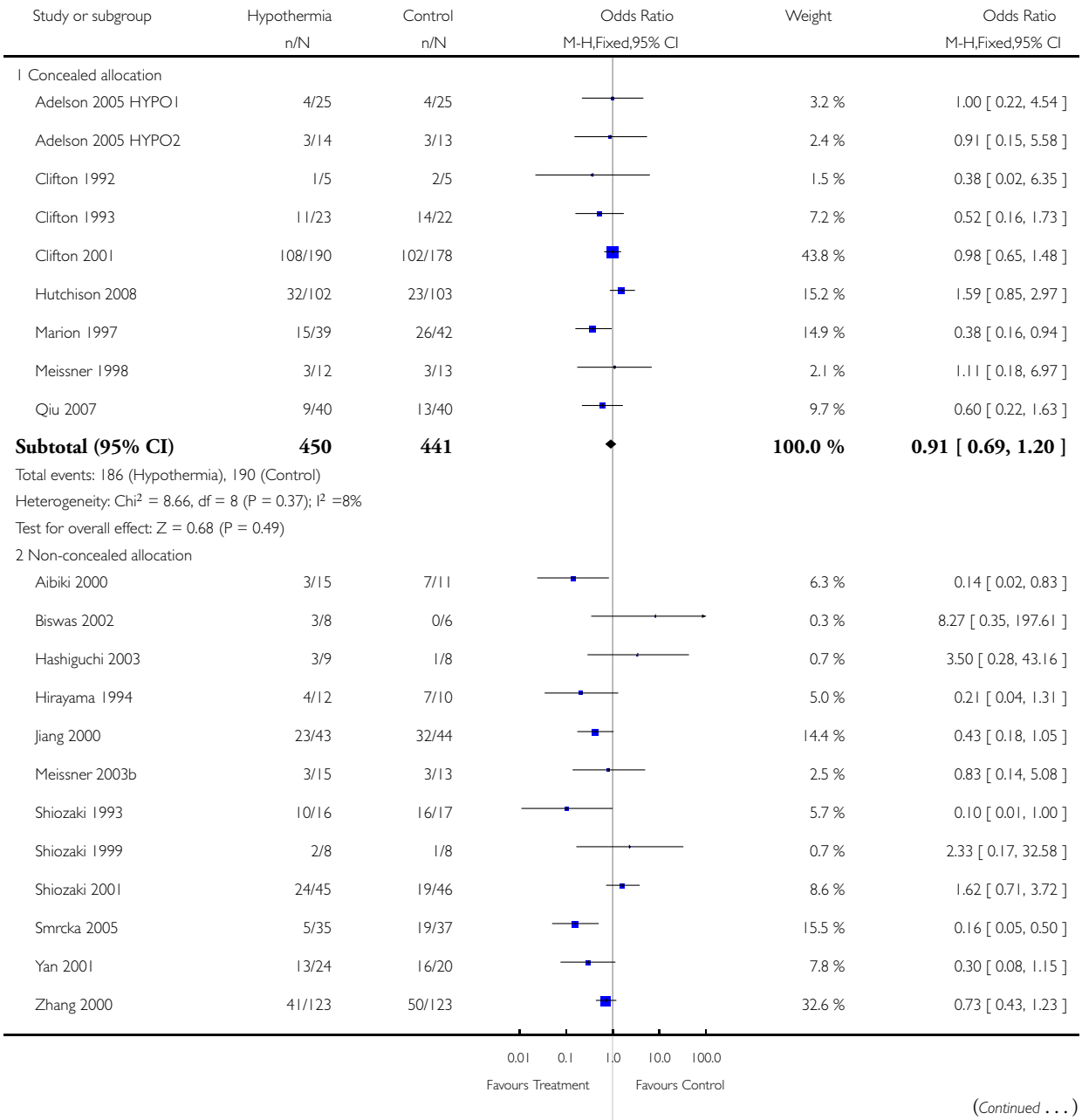
Test for overall effect: Z = 2.65 (P = 0.0080)

## Analysis 1.4. Comparison 1 Immediate hypothermia versus normothermia, Outcome 4 Unfavourable outcome stratified by trial quality.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 4 Unfavourable outcome stratified by trial quality

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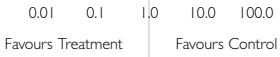
| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **353** | **343** | | **100.0 %** | **0.60 [ 0.44, 0.82 ]** |
| Total events: 134 (Hypothermia), 171 (Control) | | | | | |
| Heterogeneity: Chi² = 24.64, df = 11 (P = 0.01); I² =55% | | | | | |
| Test for overall effect: Z = 3.19 (P = 0.0014) | | | | | |




Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

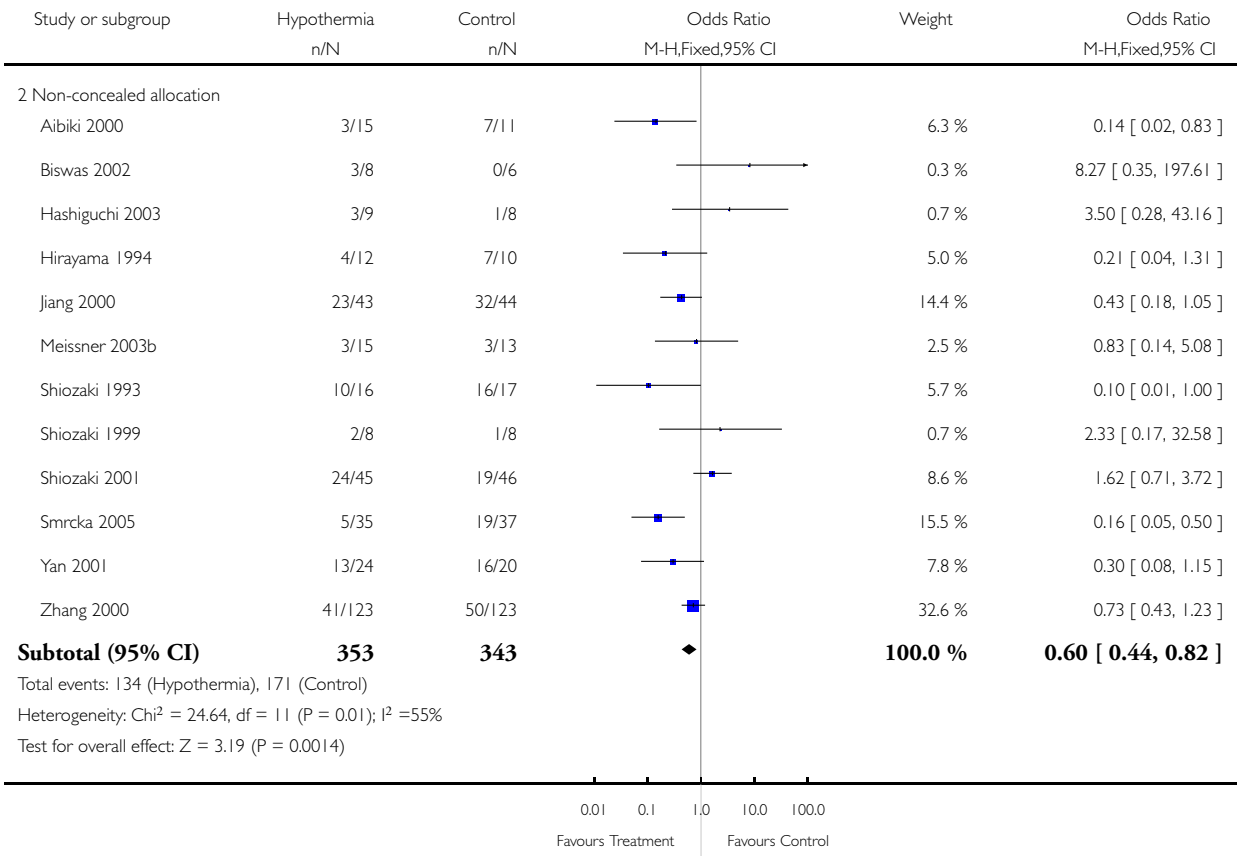
Outcome: 4 Unfavourable outcome stratified by trial quality

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Concealed allocation | | | | | |
| Adelson 2005 HYPO1 | 4/25 | 4/25 | | 3.2 % | 1.00 [ 0.22, 4.54 ] |
| Adelson 2005 HYPO2 | 3/14 | 3/13 | | 2.4 % | 0.91 [ 0.15, 5.58 ] |
| Clifton 1992 | 1/5 | 2/5 | | 1.5 % | 0.38 [ 0.02, 6.35 ] |
| Clifton 1993 | 11/23 | 14/22 | | 7.2 % | 0.52 [ 0.16, 1.73 ] |
| Clifton 2001 | 108/190 | 102/178 | | 43.8 % | 0.98 [ 0.65, 1.48 ] |
| Hutchison 2008 | 32/102 | 23/103 | | 15.2 % | 1.59 [ 0.85, 2.97 ] |
| Marion 1997 | 15/39 | 26/42 | | 14.9 % | 0.38 [ 0.16, 0.94 ] |
| Meissner 1998 | 3/12 | 3/13 | | 2.1 % | 1.11 [ 0.18, 6.97 ] |
| Qiu 2007 | 9/40 | 13/40 | | 9.7 % | 0.60 [ 0.22, 1.63 ] |
| **Subtotal (95% CI)** | **450** | **441** | | **100.0 %** | **0.91 [ 0.69, 1.20 ]** |
| Total events: 186 (Hypothermia), 190 (Control) | | | | | |
| Heterogeneity: Chi² = 8.66, df = 8 (P = 0.37); I² =8% | | | | | |
| Test for overall effect: Z = 0.68 (P = 0.49) | | | | | |

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 4 Unfavourable outcome stratified by trial quality

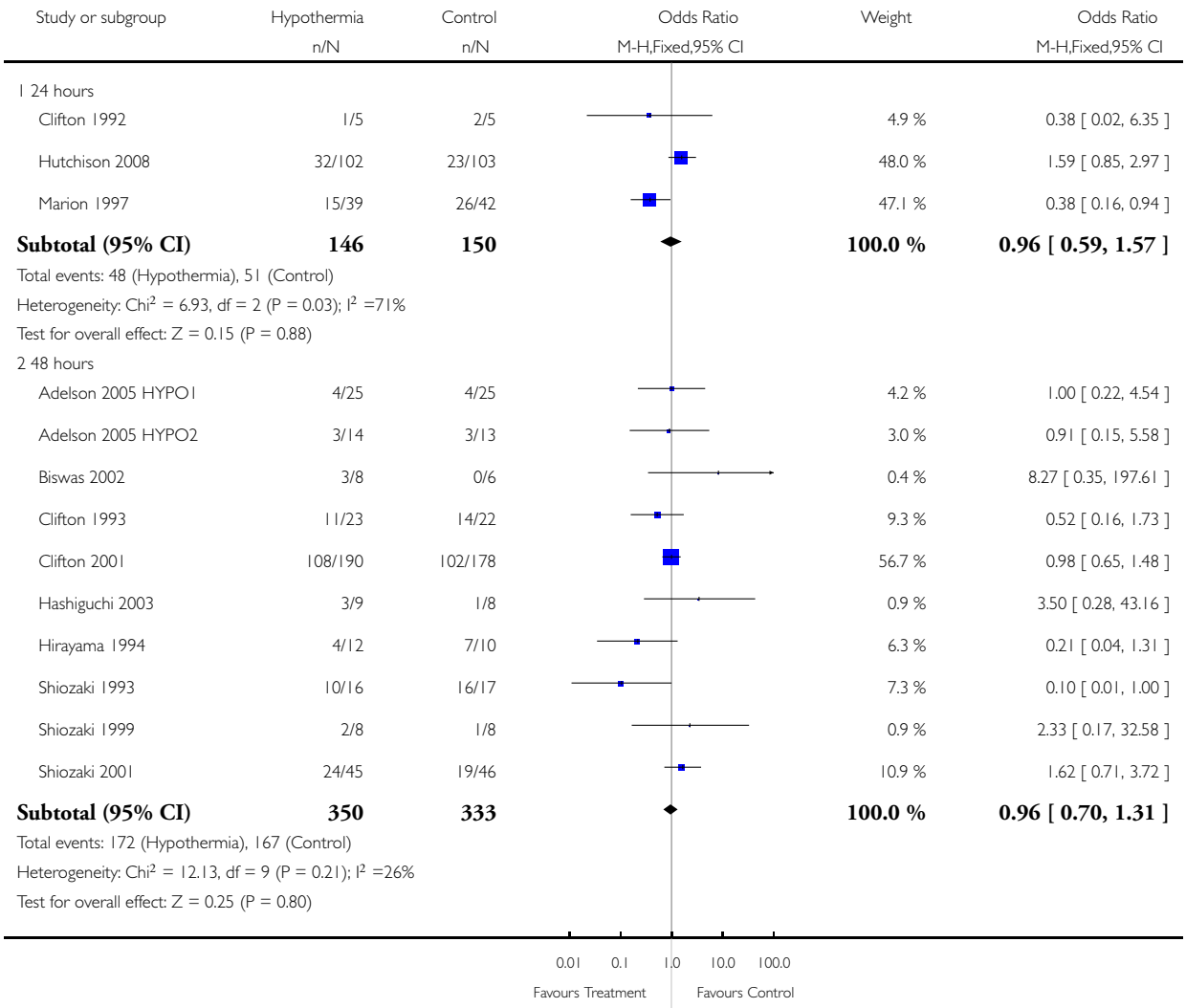


## Analysis 1.5. Comparison 1 Immediate hypothermia versus normothermia, Outcome 5 Unfavourable outcome stratified by treatment duration.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 5 Unfavourable outcome stratified by treatment duration



Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 5 Unfavourable outcome stratified by treatment duration

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 24 hours | | | | | |
| Clifton 1992 | 1/5 | 2/5 | | 4.9 % | 0.38 [ 0.02, 6.35 ] |
| Hutchison 2008 | 32/102 | 23/103 | | 48.0 % | 1.59 [ 0.85, 2.97 ] |
| Marion 1997 | 15/39 | 26/42 | | 47.1 % | 0.38 [ 0.16, 0.94 ] |
| **Subtotal (95% CI)** | **146** | **150** | | **100.0 %** | **0.96 [ 0.59, 1.57 ]** |
| Total events: 48 (Hypothermia), 51 (Control) | | | | | |
| Heterogeneity: Chi² = 6.93, df = 2 (P = 0.03); I² =71% | | | | | |
| Test for overall effect: Z = 0.15 (P = 0.88) | | | | | |


Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 5 Unfavourable outcome stratified by treatment duration

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 2 48 hours | | | | | |
| Adelson 2005 HYPO1 | 4/25 | 4/25 | | 4.2 % | 1.00 [ 0.22, 4.54 ] |
| Adelson 2005 HYPO2 | 3/14 | 3/13 | | 3.0 % | 0.91 [ 0.15, 5.58 ] |
| Biswas 2002 | 3/8 | 0/6 | | 0.4 % | 8.27 [ 0.35, 197.61 ] |
| Clifton 1993 | 11/23 | 14/22 | | 9.3 % | 0.52 [ 0.16, 1.73 ] |
| Clifton 2001 | 108/190 | 102/178 | | 56.7 % | 0.98 [ 0.65, 1.48 ] |
| Hashiguchi 2003 | 3/9 | 1/8 | | 0.9 % | 3.50 [ 0.28, 43.16 ] |
| Hirayama 1994 | 4/12 | 7/10 | | 6.3 % | 0.21 [ 0.04, 1.31 ] |
| Shiozaki 1993 | 10/16 | 16/17 | | 7.3 % | 0.10 [ 0.01, 1.00 ] |


(*Continued . . .*)

(. . . *Continued*)

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Shiozaki 1999 | 2/8 | 1/8 | | 0.9 % | 2.33 [ 0.17, 32.58 ] |
| Shiozaki 2001 | 24/45 | 19/46 | | 10.9 % | 1.62 [ 0.71, 3.72 ] |
| **Subtotal (95% CI)** | **350** | **333** | | **100.0 %** | **0.96 [ 0.70, 1.31 ]** |
| Total events: 172 (Hypothermia), 167 (Control) | | | | | |
| Heterogeneity: Chi² = 12.13, df = 9 (P = 0.21); I² =26% | | | | | |
| Test for overall effect: Z = 0.25 (P = 0.80) | | | | | |


**Analysis 1.6. Comparison 1 Immediate hypothermia versus normothermia, Outcome 6 Unfavourable outcome at various times during follow-up.**

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 6 Unfavourable outcome at various times during follow-up

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 3 months | | | | | |
| Biswas 2002 | 4/10 | 0/11 | | 0.8 % | 15.92 [ 0.73, 345.07 ] |
| Clifton 1992 | 1/5 | 2/5 | | 4.6 % | 0.38 [ 0.02, 6.35 ] |
| Clifton 1993 | 11/23 | 14/22 | | 21.6 % | 0.52 [ 0.16, 1.73 ] |
| Hirayama 1994 | 4/12 | 5/10 | | 10.5 % | 0.50 [ 0.09, 2.81 ] |
| Marion 1997 | 25/40 | 35/42 | | 37.1 % | 0.33 [ 0.12, 0.94 ] |
| Shiozaki 2001 | 24/45 | 19/46 | | 25.4 % | 1.62 [ 0.71, 3.72 ] |
| **Subtotal (95% CI)** | **135** | **136** | | **100.0 %** | **0.85 [ 0.52, 1.39 ]** |
| Total events: 69 (Hypothermia), 75 (Control) | | | | | |
| Heterogeneity: Chi² = 10.29, df = 5 (P = 0.07); I² =51% | | | | | |
| Test for overall effect: Z = 0.65 (P = 0.51) | | | | | |
| 2 6 months | | | | | |
| Aibiki 2000 | 3/15 | 7/11 | | 5.8 % | 0.14 [ 0.02, 0.83 ] |
| Biswas 2002 | 3/9 | 9/11 | | 4.9 % | 0.11 [ 0.01, 0.88 ] |
| Clifton 2001 | 108/190 | 102/178 | | 40.9 % | 0.98 [ 0.65, 1.48 ] |


(*Continued* . . . )

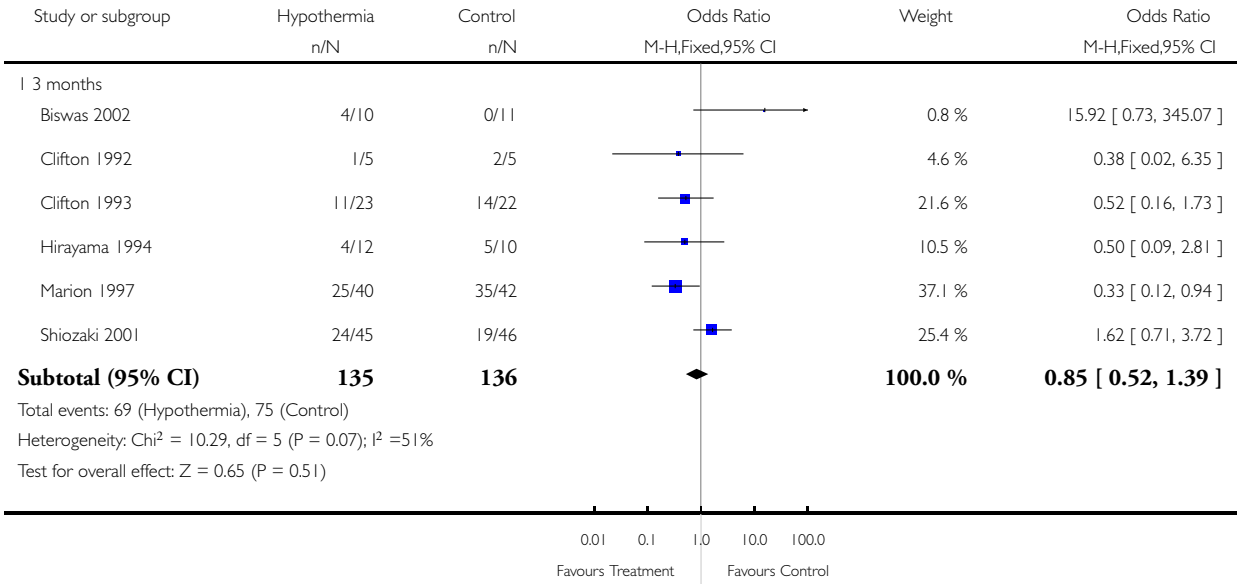
(. . . *Continued*)

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Hashiguchi 2003 | 3/9 | 1/8 | | 0.6 % | 3.50 [ 0.28, 43.16 ] |
| Hutchison 2008 | 32/102 | 23/103 | | 14.1 % | 1.59 [ 0.85, 2.97 ] |
| Marion 1997 | 18/40 | 28/42 | | 13.5 % | 0.41 [ 0.17, 1.00 ] |
| Shiozaki 1993 | 10/16 | 16/17 | | 5.2 % | 0.10 [ 0.01, 1.00 ] |
| Shiozaki 1999 | 2/8 | 1/8 | | 0.7 % | 2.33 [ 0.17, 32.58 ] |
| Smrcka 2005 | 5/35 | 19/37 | | 14.2 % | 0.16 [ 0.05, 0.50 ] |
| **Subtotal (95% CI)** | **424** | **415** | | **100.0 %** | **0.76 [ 0.57, 1.01 ]** |
| Total events: 184 (Hypothermia), 206 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 27.77, df = 8 (P = 0.00052); $I^2$ =71% | | | | | |
| Test for overall effect: Z = 1.90 (P = 0.057) | | | | | |
| 3 12 months | | | | | |
| Biswas 2002 | 3/8 | 0/6 | | 0.8 % | 8.27 [ 0.35, 197.61 ] |
| Jiang 2000 | 23/43 | 32/44 | | 36.3 % | 0.43 [ 0.18, 1.05 ] |
| Marion 1997 | 15/39 | 26/42 | | 38.0 % | 0.38 [ 0.16, 0.94 ] |
| Qiu 2007 | 9/40 | 13/40 | | 24.9 % | 0.60 [ 0.22, 1.63 ] |
| **Subtotal (95% CI)** | **130** | **132** | | **100.0 %** | **0.52 [ 0.31, 0.87 ]** |
| Total events: 50 (Hypothermia), 71 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.62, df = 3 (P = 0.31); $I^2$ =17% | | | | | |
| Test for overall effect: Z = 2.48 (P = 0.013) | | | | | |

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

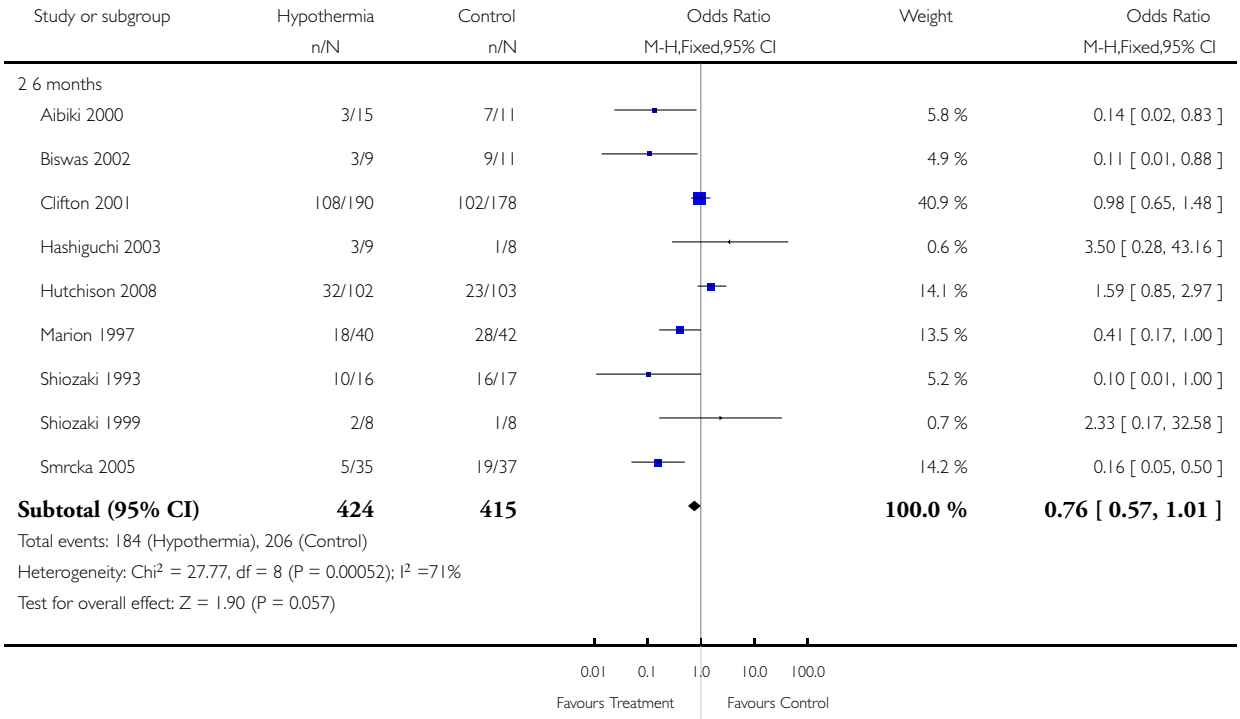
Outcome: 6 Unfavourable outcome at various times during follow-up



Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 6 Unfavourable outcome at various times during follow-up



Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 6 Unfavourable outcome at various times during follow-up

| Study or subgroup | Hypothermia n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 3 12 months | | | | | |
| Biswas 2002 | 3/8 | 0/6 | | 0.8 % | 8.27 [ 0.35, 197.61 ] |
| Jiang 2000 | 23/43 | 32/44 | | 36.3 % | 0.43 [ 0.18, 1.05 ] |
| Marion 1997 | 15/39 | 26/42 | | 38.0 % | 0.38 [ 0.16, 0.94 ] |
| Qiu 2007 | 9/40 | 13/40 | | 24.9 % | 0.60 [ 0.22, 1.63 ] |
| **Subtotal (95% CI)** | **130** | **132** | | **100.0 %** | **0.52 [ 0.31, 0.87 ]** |
| Total events: 50 (Hypothermia), 71 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.62, df = 3 (P = 0.31); $I^2$ =17% | | | | | |
| Test for overall effect: Z = 2.48 (P = 0.013) | | | | | |

## Analysis 1.7. Comparison 1 Immediate hypothermia versus normothermia, Outcome 7 Pneumonia during the treatment period.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 7 Pneumonia during the treatment period

| Study or subgroup | Treatment n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Concealed allocation | | | | | |
| Clifton 1992 | 2/5 | 2/5 | | 2.2 % | 1.00 [ 0.08, 12.56 ] |
| Clifton 1993 | 9/24 | 7/22 | | 8.2 % | 1.29 [ 0.38, 4.35 ] |
| Hutchison 2008 | 39/108 | 51/117 | | 56.3 % | 0.73 [ 0.43, 1.25 ] |
| Meissner 1998 | 6/7 | 6/6 | | 2.3 % | 0.33 [ 0.01, 9.79 ] |
| **Subtotal (95% CI)** | **144** | **150** | | **69.0 %** | **0.79 [ 0.49, 1.27 ]** |
| Total events: 56 (Treatment), 66 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.97, df = 3 (P = 0.81); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | | |
| 2 Non-concealed allocation | | | | | |
| Aibiki 2000 | 4/15 | 3/11 | | 4.6 % | 0.97 [ 0.17, 5.59 ] |
| Biswas 2002 | 0/1 | 0/1 | | 0.0 % | 0.0 [ 0.0, 0.0 ] |
| Hashiguchi 2003 | 5/9 | 0/8 | | 0.4 % | 20.78 [ 0.92, 466.97 ] |
| Jiang 2000 | 16/43 | 14/44 | | 15.6 % | 1.27 [ 0.52, 3.08 ] |
| Shiozaki 1993 | 9/13 | 6/9 | | 3.9 % | 1.13 [ 0.18, 6.93 ] |
| Shiozaki 1999 | 5/8 | 1/8 | | 0.7 % | 11.67 [ 0.92, 147.56 ] |
| Shiozaki 2001 | 21/43 | 6/40 | | 5.7 % | 5.41 [ 1.89, 15.52 ] |
| **Subtotal (95% CI)** | **132** | **121** | | **31.0 %** | **2.47 [ 1.44, 4.23 ]** |
| Total events: 60 (Treatment), 30 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 9.34, df = 5 (P = 0.10); $I^2$ =46% | | | | | |
| Test for overall effect: Z = 3.29 (P = 0.0010) | | | | | |
| **Total (95% CI)** | **276** | **271** | | **100.0 %** | **1.31 [ 0.93, 1.86 ]** |
| Total events: 116 (Treatment), 96 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 18.19, df = 9 (P = 0.03); $I^2$ =51% | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | |

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 7 Pneumonia during the treatment period

| Study or subgroup | Treatment n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Concealed allocation | | | | | |
| Clifton 1992 | 2/5 | 2/5 | | 2.2 % | 1.00 [ 0.08, 12.56 ] |
| Clifton 1993 | 9/24 | 7/22 | | 8.2 % | 1.29 [ 0.38, 4.35 ] |
| Hutchison 2008 | 39/108 | 51/117 | | 56.3 % | 0.73 [ 0.43, 1.25 ] |
| Meissner 1998 | 6/7 | 6/6 | | 2.3 % | 0.33 [ 0.01, 9.79 ] |
| **Subtotal (95% CI)** | **144** | **150** | | **69.0 %** | **0.79 [ 0.49, 1.27 ]** |
| Total events: 56 (Treatment), 66 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 0.97, df = 3 (P = 0.81); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.96 (P = 0.34) | | | | | |


Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 7 Pneumonia during the treatment period

| Study or subgroup | Treatment n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 2 Non-concealed allocation | | | | | |
| Aibiki 2000 | 4/15 | 3/11 | | 4.6 % | 0.97 [ 0.17, 5.59 ] |
| Biswas 2002 | 0/1 | 0/1 | | 0.0 % | 0.0 [ 0.0, 0.0 ] |
| Hashiguchi 2003 | 5/9 | 0/8 | | 0.4 % | 20.78 [ 0.92, 466.97 ] |
| Jiang 2000 | 16/43 | 14/44 | | 15.6 % | 1.27 [ 0.52, 3.08 ] |
| Shiozaki 1993 | 9/13 | 6/9 | | 3.9 % | 1.13 [ 0.18, 6.93 ] |
| Shiozaki 1999 | 5/8 | 1/8 | | 0.7 % | 11.67 [ 0.92, 147.56 ] |
| Shiozaki 2001 | 21/43 | 6/40 | | 5.7 % | 5.41 [ 1.89, 15.52 ] |


(*Continued . . .*)

(. . . *Continued*)

| Study or subgroup | Treatment n/N | Control n/N | Odds Ratio M-H,Fixed,95% CI | Weight | Odds Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| **Subtotal (95% CI)** | **132** | **121** | ◆ | **31.0 %** | **2.47 [ 1.44, 4.23 ]** |
| Total events: 60 (Treatment), 30 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 9.34, df = 5 (P = 0.10); $I^2$ =46% | | | | | |
| Test for overall effect: Z = 3.29 (P = 0.0010) | | | | | |


# APPENDICES

## Appendix 1. Latest search strategy

**Injuries Group's Specialised Register (searched 12 January 2009)**
((injur* or trauma* or lesion* or damage* or wound* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*) and (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit*)) and (hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*)

**CENTRAL (*The Cochrane Library 2008, Issue 4)***
#1MeSH descriptor Craniocerebral Trauma explode all trees
#2MeSH descriptor Cerebrovascular Trauma explode all trees
#3MeSH descriptor Brain Edema explode all trees
#4(brain or cerebral or intracranial) near3 (oedema or edema or swell*)
#5MeSH descriptor Glasgow Coma Scale explode all trees
#6MeSH descriptor Glasgow Outcome Scale explode all trees
#7MeSH descriptor Unconsciousness explode all trees
#8glasgow near3 (coma or outcome) near3 (score or scale)
#9(Unconscious* or coma* or concuss* or 'persistent vegetative state') near 3 (injur* or trauma* or damag* or wound* or fracture*)
#10"Rancho Los Amigos Scale"
#11(head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near3 (injur* or trauma* or damag* or wound* or fracture* or contusion*)
#12Diffuse near3 axonal near3 injur*
#13(head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) near3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)
#14(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15MeSH descriptor Hypothermia, Induced explode all trees
#16MeSH descriptor Cryotherapy explode all trees
#17MeSH descriptor Body Temperature explode all trees
#18hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*
#19(#15 OR #16 OR #17 OR #18)
#20(#14 AND #19)
#21neonat*
#22(#20 AND NOT #21)

**MEDLINE STRATEGY (1966 to January 2009)**
1.exp Craniocerebral Trauma/
2.exp Brain Edema/

3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Unconsciousness/
6.exp Cerebrovascular Trauma/
7.((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
8.((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ti,ab.
9.(Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
10."rancho los amigos scale".ti,ab.
11.("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
12.((brain or cerebral or intracranial) adj3 (oedema or edema or swell$)).ab,ti.
13.((unconscious$ or coma$ or concuss$ or 'persistent vegetative state') adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab.
14.or/1-13
15.(randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
16.clinical trial.pt.
17.randomized controlled trial.pt.
18.15 or 16 or 17
19.exp models, animal/
20.exp Animals/
21.exp Animal Experimentation/
22.exp Disease Models, Animal/
23.exp Animals, Laboratory/
24.or/19-23
25.Humans/
26.24 not 25
27.18 not 26
28.14 and 27
29.exp Hypothermia, Induced/
30.exp Cryotherapy/
31.exp Body Temperature/
32.(hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*).ab,ti.
33.or/29-32
34.neonat*.ab,ti.
35.33 not 34
36.28 and 35
PUBMED Searched 21-05-08 (last 90 days)
7 records retrieved
#1Craniocerebral Trauma [mh] OR Brain Edema [mh] OR Glasgow Coma Scale [mh] OR Glasgow Outcome Scale [mh] OR Unconsciousness [mh] OR Cerebrovascular Trauma [mh] OR ((head or cranial or cerebral or brain* or intra-cranial or inter-cranial) AND (haematoma* or hematoma* or haemorrhag* or hemorrhage* or bleed* or pressure)) OR (Glasgow AND scale) OR ("diffuse axonal injury" OR "diffuse axonal injuries") or ("persistent vegetative state") OR ((unconscious* OR coma* OR concuss*) AND (injury* OR injuries OR trauma OR damage OR damaged OR wound* OR fracture* OR contusion* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed* OR pressure))
#2(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh]) NOT ((models, animal[mh] OR Animals[mh] OR Animal Experimentation[mh] OR Disease Models, Animal[mh] OR Animals, Laboratory[mh]) NOT (Humans[mh]))
#31 and 2
#4("Hypothermia, Induced"[Mesh] OR "Cryotherapy"[Mesh]) OR "Body Temperature"[Mesh]
#5hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat* Field: Title/Abstract

#64 or 5
#7Neonat* Field: Title/Abstract
#86 not 7
#93 and 8

**EMBASE 1980 to January 2009**
1.exp Brain Injury/
2.exp Brain Edema/
3.exp Glasgow Coma Scale/
4.exp Glasgow Outcome Scale/
5.exp Rancho Los Amigos Scale/
6.exp Unconsciousness/
7.((brain or cerebral or intracranial) adj3 (oedema or edema or swell$)).ab,ti.
8.((head or crani$ or cerebr$ or capitis or brain$ or forebrain$ or skull$ or hemispher$ or intra-cran$ or inter-cran$) adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$ or contusion$)).ab,ti.
9.(Glasgow adj3 (coma or outcome) adj3 (scale$ or score$)).ab,ti.
10.Rancho Los Amigos Scale.ab,ti.
11.((unconscious$ or coma$ or concuss$ or 'persistent vegetative state') adj3 (injur$ or trauma$ or damag$ or wound$ or fracture$)).ti,ab.
12.Diffuse axonal injur$.ab,ti.
13.((head or crani$ or cerebr$ or brain$ or intra-cran$ or inter-cran$) adj3 (haematoma$ or hematoma$ or haemorrhag$ or hemorrhag$ or bleed$ or pressure)).ab,ti.
14.or/1-13
15.exp animal model/
16.Animal Experiment/
17.exp ANIMAL/
18.exp Experimental Animal/
19.15 or 16 or 17 or 18
20.Human/
21.19 not 20
22.(randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
23.exp clinical trial/
24.22 or 23
25.24 not 21
26.14 and 25
27.exp INDUCED HYPOTHERMIA/
28.exp PROFOUND INDUCED HYPOTHERMIA/
29.exp CRYOTHERAPY/
30.exp Body Temperature/
31.(hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*).ab,ti.
32.27 or 28 or 29 or 30 or 31
33.neonat*.ab,ti.
34.32 not 33
35.26 and 34

**Controlled Trials metaRegister of trials (mRCT) http://www.controlled-trials.com/mrct/ (Searched 12 January 2009)**
((injur* or trauma* or damage*) and (head or crani* or brain* or forebrain* or intracran*)) and (hypotherm* or normotherm* or cool* or cold* or temperature* or cryother*)

**ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to Jan 2009 and Conference Proceedings Citation Index- Science (CPCI-S) 1990 to Jan 2009. (searched 12 January 2009)**

1.Topic=((injur* or trauma* or lesion* or damage* or wound* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*) AND (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit*)) AND Topic=(hypotherm* or normotherm* or cool* or cold* or temperature* or cryother* or cryogen* or cryotreat*) NOT Topic=(neonat*)
2.Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR controlled trial OR clinical trial) NOT Topic=(animal model* OR Animals OR Animal Experiment* OR Laboratory animals* or animal disease model*)
3.1 and 2

**ZETOC (searched 12 January 2009)**
Hypotherm* head injur* trial*
Hypotherm* head injur* random*
Hypotherm* head injur* control*

Hypotherm* brain injur* trial*
Hypotherm* brain injur* random*
Hypotherm* brain injur* control*

Hypotherm* head trauma* trial*
Hypotherm* head trauma* random*
Hypotherm* head trauma* control*

Hypotherm* brain trauma* trial*
Hypotherm* brain trauma* random*
Hypotherm* brain trauma* control*

## Appendix 2. Original search strategy

For the initial version of the review the following search was done:
The Specialist Trials Register for the Injuries Group was searched 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 as follows, to identify all potential RCTs involving human head injury and temperature control from 1980 onwards :
001 exp head injury/
002 pneumocephalus/
003 cerebrospinal fluid/
004 otorrhea/
005 exp skull fracture/
006 exp spine fracture/
007 Cerebrospinal Fluid Rhinorrhea/
008 exp asphyxia/
009 exp spine injury/
010 helmet/
011 brain protection/
012 brain edema/
013 exp brain hemorrhage/
014 brain hypoxia/
015 coma/
016 persistent vegetative state/
017 Traumatic Epilepsy/
018 or/1-17

019 (head or brain or cerebr$ or skull or crani$ or spin$).tw.
020 (wound$ or injur$ or trauma$ or oedema$ or edema$).tw.
021 damage$.tw.
022 20 or 21
023 19 and 22
024 18 or 23
025 human/
026 “888”.tg.
027 25 or 26
028 Nonhuman/
029 “777”.tg.
030 28 or 29
031 27 and 30
032 30 not 31
033 clinical trial/
034 Multicenter Study/
035 phase 2 clinical trial/
036 phase 3 clinical trial/
037 Phase 4 Clinical Trial/
038 Randomized Controlled Trial/
039 controlled study/
040 meta analysis/
041 crossover procedure/
042 double blind procedure/
043 Single Blind Procedure/
044 randomization/
045 Major Clinical Study/
046 placebo/
047 drug comparison/
048 clinical study/
049 “0197”.tg.
050 “0150”.tg.
051 “03738”.dc.
052 (clin$ adj25 trial$).tw.
053 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
054 placebo$.tw.
055 random$.tw.
056 control$.tw.
057 or/33-56
058 24 not 32
059 Induced Hypothermia/
060 Profound Induced Hypothermia/
061 exp temperature/
062 exp low temperature procedures/
063 cold/
064 cold air/
065 cold exposure/
066 (hypotherm$ or normotherm$ or cool$ or cold$ or temperature$).tw.
067 or/59-66
068 58 and 67
069 68 and 57

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

## WHAT'S NEW

Last assessed as up-to-date: 11 January 2009.

| | | |
|---|---|---|
| 26 January 2009 | New citation required and conclusions have changed | Review updated; search updated to 12 January 2009.<br>Data from one new study is included (Hutchinson 2008).<br>The results of the review have been amended accordingly.<br>One further study was excluded (Gal 2002). |

## HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 1999

| | | |
|---|---|---|
| 31 October 2008 | New citation required and conclusions have changed | Eight new trials are included in this update. The results of the review have been amended accordingly.<br>One trial currently in 'studies awaiting assessment' (Hutchison 2008a) was identified after the search was completed for this update. Data from this trial will be included in the review for Issue 2, 2009.<br>The title has been changed from 'Therapeutic hypothermia for head injury' to 'Hypothermia for traumatic head injury'.<br>The authors of the review have changed. |
| 9 July 2008 | Amended | The version of this review published in July 2008 mistakenly included three additional trials in the table of included studies and references sections.<br>Data from these three studies were not included in the review. The text of the review is the same as the 28 July 2004 update. |
| 14 May 2008 | Amended | Converted to new review format. |

(*Continued*)

| | | |
|---|---|---|
| 28 July 2004 | New search has been performed | Substantive amendment. New studies found and included or excluded.<br>Two more trials have been included, and one added to the awaiting assessment list as we have not been able to obtain a copy of the trial.<br>Conclusions have been reviewed and compared to those found in a review of the topic in JAMA. |
| 12 November 2001 | New search has been performed | Four studies were included, which were published since the original version of this review.<br>Quantitative synthesis of the incidence of pulmonary infections was conducted in the 2001 update. |

## CONTRIBUTIONS OF AUTHORS

David Signorini wrote the protocol, performed the searches and reviewed the titles and abstracts, extracted the data, performed the analyses and wrote the draft of the review. Phil Alderson (PA) reviewed the manuscripts of potential trials, extracted the data and edited the draft review.

For the 2001 update, the Injuries Group performed the search and screened studies. PA and Chirag Gadkary assessed eligibility, extracted data, performed the analysis and redrafted the text.

For the 2004 update, the Injuries Group performed the search and screened studies. PA and the Injuries Group extracted data, and PA performed the analysis and rewrote the text.

For the 2008 update, the search was carried out by Karen Blackhall of the Cochrane Injuries Group. Emma Sydenham (ES) and Ian Roberts (IR) assessed trial eligibility and applied the selection criteria. ES extracted data, and IR checked for accuracy. ES updated the text of the review. IR and ES performed the analysis and edited the manuscript. PA checked the final manuscript of the update.

Karen Blackhall performed the search for the 2009 update. Emma Sydenham (ES) and Ian Roberts (IR) assessed trial eligibility and applied the selection criteria. ES extracted the data, and IR checked the extracted data for accuracy. ES updated the text of the review. IR and ES performed the analysis and edited the manuscript. PA checked the final manuscript of the update.

## DECLARATIONS OF INTEREST

None known.

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### External sources


- CG was supported by the Doris Duke Research Fellowship, USA.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The 2008 update of this review evaluated study quality by allocation concealment only. The incidence of pneumonia was also stratified by study quality.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Craniocerebral Trauma [mortality; *therapy]; *Hypothermia, Induced [adverse effects]; Randomized Controlled Trials as Topic

### MeSH check words

Humans