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Lewis SR, Baker PE, Andrews PJD, Cheng A, Deol K, Hammond N, Saxena M.
Interventions to reduce body temperature to 35 °C to 37 °C in adults and children with traumatic brain injury.
Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD006811.
DOI: [10.1002/14651858.CD006811.pub4](https://doi.org/10.1002/14651858.CD006811.pub4).

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[Intervention Review]

Interventions to reduce body temperature to 35 °C to 37 °C in adults and children with traumatic brain injury

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Contact: Philip E Baker, philipbaker8@gmail.com.**Editorial group:** Cochrane Injuries Group.**Publication status and date:** Edited (conclusions changed), published in Issue 10, 2020.

Citation: Lewis SR, Baker PE, Andrews PJD, Cheng A, Deol K, Hammond N, Saxena M. Interventions to reduce body temperature to 35 °C to 37 °C in adults and children with traumatic brain injury. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD006811. DOI: [10.1002/14651858.CD006811.pub4](https://doi.org/10.1002/14651858.CD006811.pub4).

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ABSTRACT

Background

Traumatic brain injury (TBI) is a major cause of death and disability, with an estimated 5.5 million people experiencing severe TBI worldwide every year. Observational clinical studies of people with TBI suggest an association between raised body temperature and unfavourable outcome, although this relationship is inconsistent. Additionally, preclinical models suggest that reducing temperature to 35 °C to 37.5 °C improves biochemical and histopathological outcomes compared to reducing temperature to a lower threshold of 33 °C to 35 °C. It is unknown whether reducing body temperature to 35 °C to 37.5 °C in people admitted to hospital with TBI is beneficial, has no effect, or causes harm. This is an update of a review last published in 2014.

Objectives

To assess the effects of pharmacological interventions or physical interventions given with the intention of reducing body temperature to 35 °C to 37.5 °C in adults and children admitted to hospital after TBI.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Web of Science, and PubMed on 28 November 2019. We searched clinical trials registers, grey literature and references lists of reviews, and we carried out forward citation searches of included studies.

Selection criteria

We included randomised controlled trials (RCTs) with participants of any age admitted to hospital following TBI. We included interventions that aimed to reduce body temperature to 35 °C to 37.5 °C: these included pharmacological interventions (such as paracetamol, or non-steroidal anti-inflammatory drugs), or physical interventions (such as surface cooling devices, bedside fans, or cooled intravenous fluids). Eligible comparators were placebo or usual care.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, and assessed risks of bias. We assessed the certainty of the evidence with GRADE.

Main results

We included one RCT with 41 participants. This study recruited adult participants admitted to two intensive care units in Australia, and evaluated a pharmacological intervention. Researchers gave participants 1 g paracetamol or a placebo intravenously at four-hourly intervals for 72 hours.

We could not be certain whether intravenous paracetamol influenced mortality at 28 days (risk ratio 2.86, 95% confidence interval 0.32 to 25.24). We judged the evidence for this outcome to be very low certainty, meaning we have very little confidence in this effect estimate, and the true result may be substantially different to this effect. We downgraded the certainty for imprecision (because the evidence was from a single study with very few participants), and study limitations (because we noted a high risk of selective reporting bias). This study was otherwise at low risk of bias.

The included study did not report the primary outcome for this review, which was the number of people with a poor outcome at the end of follow-up (defined as death or dependency, as measured on a scale such as the Glasgow Outcome Score), or any of our secondary outcomes, which included the number of people with further intracranial haemorrhage, extracranial haemorrhage, abnormal intracranial pressure, or pneumonia or other serious infections.

The only other completed trial that we found was of a physical intervention that compared advanced fever control (using a surface cooling device) versus conventional fever control in 12 participants. The trial was published as an abstract only, with insufficient details to allow inclusion, so we have added this to the 'studies awaiting classification' section, pending further information from the study authors or publication of the full study report.

We identified four ongoing studies that will contribute evidence to future updates of the review if they measure relevant outcomes and, in studies with a mixed population, report data separately for participants with TBI.

Authors' conclusions

One small study contributed very low-certainty evidence for mortality to this review. The uncertainty is largely driven by limited research into reduction of body temperature to 35 °C to 37.5 °C in people with TBI. Further research that evaluates pharmacological or physical interventions, or both, may increase certainty in this field. We propose that future updates of the review, and ongoing and future research in this field, incorporate outcomes that are important to the people receiving the interventions, including side effects of any pharmacological agent (e.g. nausea or vomiting), and discomfort caused by physical therapies.

PLAIN LANGUAGE SUMMARY

Treatments to reduce body temperature to 35 °C to 37.5 °C in people who are in hospital after a traumatic brain injury

Background

Traumatic brain injury occurs as a result of direct impact to the brain, such as after a road traffic accident or fall from a height. It is a major cause of death and disability, experienced by about 5.5 million people worldwide every year. Damage occurs in two stages: firstly, at the time of impact; and secondly, in the hours and weeks following injury. Management of a traumatic brain injury aims to reduce the impact of this secondary damage. There is some evidence to suggest that people with a normal body temperature after injury may have a better outcome than those with a higher temperature.

Review question

This review assessed whether medicines or physical cooling treatments that do not use medicine, given to reduce body temperature to between 35 °C and 37.5 °C, affect outcomes in adults or children who are in hospital after a traumatic brain injury.

Search date

We searched for randomised controlled trials (RCTs) up to 28 November 2019. RCTs assign participants to treatment group by chance, and provide the most reliable type of evidence.

Study characteristics

We found only one small study with 41 people who had recently been admitted to the intensive care unit after a traumatic head injury. This study assessed the effects of paracetamol, given intravenously (through a needle or tube inserted into a vein) for 72 hours, compared to an intravenous salt solution that was disguised to look like the paracetamol solution.

We found no full reports of studies that gave people with traumatic brain injury other medicines or physical cooling treatments, such as blankets, fans, or ice to cool the surface of the skin, or cooled intravenous fluids. We found a short report about one very small study of a physical cooling treatment. The report did not give enough information for us to include its data, but we may include it in future if more information becomes available.

We also found four ongoing studies, which may provide more evidence for the review once they have completed. Some studies include participants who have other types of brain injury. We will only be able to include these studies in the review if they report the findings for people with traumatic brain injury separately from people with other conditions.

Key results

We were not sure whether paracetamol affected the number of people who died within 28 days of injury. This study did not report information on the outcomes of interest to us, which included: whether people had a poor outcome (defined as death or dependency); additional serious bleeding inside the brain; bleeding of the head outside the brain; increased pressure within the skull (intracranial pressure); pneumonia or other serious infections.

Certainty of the evidence

Although the study that provided the data generally appeared to use good methods, we judged it to have a high risk of bias because the study authors did not record in advance that they planned to report on the number of people who died, even though they had shared their study plans before they started the study. Having only one study, with very few participants, means that we cannot be certain whether the results would be the same in larger studies with more people.

We judged the evidence for death to be very low certainty. This means we are not very confident about the key results in this review. The true effect of treatments may be very different from the key results reported here.

Conclusions

We are uncertain of the effects of medicines and other physical cooling treatments to reduce body temperature to 35 °C to 37.5 °C, when given to people in hospital after a traumatic head injury. More studies are needed to assess this question. In future updates, we will assess the side effects of treatments, such as nausea and vomiting, or discomfort, and we hope that ongoing and future studies will also look at these important outcomes.

SUMMARY OF FINDINGS

Summary of findings 1. Cooling to 35 °C to 37.5 °C for traumatic brain injury: pharmacological interventions

Cooling to 35 °C to 37.5 °C for traumatic brain injury: pharmacological interventions

Population: adults with traumatic brain injury

Setting: intensive care units in Australia

Intervention: 1 g paracetamol IV

Comparison: saline IV (placebo control)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with pharmacological intervention: 1 g paracetamol IV			
Poor outcome at the end of follow-up	Study population		Not estimable	—	—
	—	—			
Death from all causes during the follow-up period (28 days)	Study population		RR 2.86 (0.32 to 25.24)	41 (1 study)	⊕⊕⊕⊕ VERY LOW^a
	50 per 1000	143 per 1000 (16 to 1000)			
Serious intracranial haemorrhage	Study population		Not estimable	—	—
	—	—			
Extracranial haemorrhage	Study population		Not estimable	—	—
	—	—			
Abnormal intracranial pressure	Study population		Not estimable	—	—
	—	—			
Pneumonia or other serious infection	Study population		Not estimable	—	—
	—	—			

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IV:** intravenous(ly); **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aWe downgrade by three levels: two levels for imprecision owing to the very small sample size in a single study, and one level owing to study limitations

BACKGROUND

Description of the condition

Traumatic brain injury (TBI) is a major cause of death and disability amongst a predominantly young population, with an estimated 5.5 million people experiencing severe TBI worldwide every year ([Dewan 2018](#)). A recent study estimated that falls are the leading cause of TBI worldwide, with motor vehicle road injuries consistently the second most prevalent cause ([GBD 2019](#)). The World Health Organization Global Burden of Disease Project identified road traffic injuries as the eighth leading cause of death worldwide in 2016, up from tenth place in 2000, with road traffic injuries consistently in the top three leading causes of death in the age group five to 49 years ([WHO 2018](#)).

TBI can be confined to one area of the brain (focal injury), or can be more widespread in nature (diffuse injury). The damage done during TBI can be split into primary brain injury, which occurs at the time of the injury and is irreversible, and secondary brain injury, which occurs after the initial insult. Many people with TBI develop a fever and this may worsen the effects of the secondary injury. Secondary injury is the result of multiple reactive processes occurring after the primary injury and occurs over hours to weeks. The mainstay of managing people with TBI is to reduce the secondary injury, particularly within the 24 hours following the primary injury, to limit the extent of future neurological injury.

TBI is an important issue that affects many people worldwide. There is, however, an important lack of coherent evidence about effective therapies for the acute care of these people ([Carney 2017](#); [Lewis 2017](#)).

Description of the intervention

Targeted temperature management aims to maintain or achieve a different body temperature in order to improve clinical outcomes. Reducing body temperature, which may also be referred to as therapeutic hypothermia, has been shown to have a neuroprotective effect after cardiac arrest ([Arrich 2016](#)), and perinatal birth asphyxia ([Jacobs 2013](#)). Research into reducing body temperature for TBI has focused on cooling between 33 °C to 35 °C and below 33 °C. Results from these studies have suggested that cooling to below 33 °C confers additional risk that outweighs the benefits, whilst cooling to between 33 °C and 35 °C may confer some benefit. To date, however, clinical trials have yielded heterogeneous results ([Lewis 2017](#)).

Whilst cooling to between 33 °C and 35 °C may be beneficial, this intervention is most likely to be used where advanced prehospital trauma care, intensive care facilities, and skilled staff are readily available. In contrast, reducing body temperature to no less than 35 °C with pharmacological or physical cooling methods can be easily administered in any setting. If effective, this could benefit a large proportion of the global burden of TBI ([Andrews 2006](#)).

In this review, we focus on targeted temperature management in which interventions are given with the intention of reducing body temperature to 35 °C to 37.5 °C. This includes interventions that are administered with the intention of lowering body temperature to below normal (less than 36 °C but above 35 °C), and interventions that are given to maintain temperature within a range that is above 36 °C but below 37.5 °C (which may also be referred to as normothermia); interventions may be given to people

who present with an elevated temperature or fever as a result of the TBI, or to people who have normal body temperature. Examples of therapies that may achieve a body temperature of 35 °C to 37.5 °C include pharmacological interventions (for example, paracetamol, acetaminophen, nonsteroidal anti-inflammatory drugs) and physical interventions (for example, bedside fans, tepid sponging, ice packs, cooling blankets).

How the intervention might work

The aim of TBI management is to reduce the secondary injury that occurs after the primary insult. Secondary injury is a complex cascade of changes on a gross cellular and molecular level. The fundamental principles of reducing secondary injury are the alleviation of increased intracranial pressure and avoidance of hypotension and hypoxia. Hypothermia reduces the rate of cerebral oxygen consumption. This decreases tissue oxygen demand, prevents hypoxia, and reduces cerebral blood flow, preventing raised intracranial pressure.

Observational data from clinical cohort studies suggest that people with TBI who have an elevated body temperature may have a worse outcome than those who have a normal body temperature ([Geffroy 2004](#); [Jiang 2002](#); [Li 2012](#)), but this relationship is inconsistent ([Andrews 2006](#); [Jones 1994](#); [Stocchetti 2002](#)). Furthermore, in preclinical models, reducing body temperature to no less than 35 °C appears to improve biochemical and histopathological outcomes compared to reducing body temperature to a lower range between 33 °C and 35 °C ([Chatzipanteli 2007](#); [Dietrich 1996](#)).

Why it is important to do this review

The Brain Trauma Foundation does not make recommendations regarding interventions to reduce body temperature to no less than 35 °C after TBI ([Carney 2017](#)), reflecting the lack of evidence for this intervention. At present, we believe that interventions for this purpose, as outlined above, are used in an ad hoc fashion after TBI. We endeavoured to search for randomised controlled trials that explored the effects of reducing body temperature to 35 °C to 37.5 °C on outcomes following TBI. This systematic review aims to assess the relationship between these imposed modest changes in body temperature and outcome after TBI, and to determine whether there is any clear evidence that such a modest temperature reduction is beneficial, has no effect, or causes harm.

This is an update of a review last published in 2014; the previous version of this review found no studies that met the inclusion criteria ([Saxena 2014](#)). This review aims to identify the latest evidence to address this uncertainty.

OBJECTIVES

To assess the effects of pharmacological interventions or physical interventions given with the intention of reducing body temperature to 35 °C to 37.5 °C in adults and children admitted to hospital after TBI.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included abstracts of RCTs only if they reported sufficient information for us

to judge eligibility based on study design, types of participants, and types of intervention.

Types of participants

We included participants of any age admitted to hospital following TBI; we included any severity of TBI. We only included studies with a mixed population if it was possible to extract data specifically for participants who had a TBI.

Types of interventions

We included any pharmacological or physical intervention given with the intention of reducing body temperature to 35 °C to 37.5 °C. These interventions could be given regardless of whether the participant had an elevated or normal body temperature, and were compared to a placebo or to usual care, as defined by the study authors.

We excluded all studies that aimed to manage temperatures below 35 °C; these studies are evaluated in [Lewis 2017](#). We excluded studies in which cooling therapies crossed the threshold of 35 °C (for example, cooling ranges between 36 °C and 34 °C).

Examples of eligible pharmacological interventions included acetaminophen, paracetamol, nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors, given by any route.

Examples of eligible physical interventions included bedside fans, sponging, fluid or air-filled devices applied to body surfaces (for example, blankets, neck-collars, helmets or hoods), ice-water lavage, intravenous fluid administration, and intravenous cooling catheters.

Pharmacological interventions and physical interventions represented two distinct comparisons, and we aimed to analyse data separately for each comparison group.

Types of outcome measures

Primary outcomes

- Poor outcome at the end of follow up: this is defined as death or dependency as measured by the Glasgow Outcome Score (GOS), or an equivalent method in which it is clear how many people are dependent and how many are independent at the end of the follow-up period. On the 5-point GOS, scores of one to three represent poor outcome - that is, death, persistent vegetative state (severe damage with prolonged state of unresponsiveness and a lack of higher mental functions), and severe disability (severe injury with permanent need for help with daily living). This is the most important outcome, as the aim of treatment should not only be to prevent death, but also to improve the quality of a person's survival.

Secondary outcomes

- Death from all causes during the follow-up period.
- Further serious intracranial haemorrhage: this is defined as the need for operative intervention (for example, evacuation of subdural or extradural haematoma) occurring during the period in which the intervention is given.
- Extradural haemorrhage: defined as the need for transfusion of more than two units of packed red blood cells within a 24-hour

period occurring during the period in which the intervention is given, owing to haemorrhage on the exterior of the skull.

- Abnormal intracranial pressure: defined as an intracranial pressure of more than 20 mmHg, measured by an intracranial pressure monitor during the period in which the intervention is given.
- Pneumonia or other serious infections during the follow-up period.

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies, as outlined in Chapter 4 of the *Cochrane Handbook of Systematic Reviews of Interventions* ([Lefebvre 2019](#)). We applied no restrictions regarding language or publication status. SL searched the following databases for relevant trials:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2019; Issue 11);
- MEDLINE (Ovid SP: 1946 to 28 November 2019);
- Embase (Ovid SP; 1974 to 28 November 2019);
- Web of Science (SCI-EXPANDED; 1900 to 28 November 2019);
- PubMed (28 November 2019).

We developed a subject-specific search strategy in MEDLINE and other listed databases. The search strategy was developed in consultation with the Information Specialist for the Cochrane Injuries Group. Search strategies can be found in [Appendix 1](#).

SL searched the following clinical trial registers for ongoing and unpublished trials.

- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp on 19 December 2019).
- ClinicalTrials.gov (www.clinicaltrials.gov on 3 February 2020).

Searching other resources

SL carried out forward citation searches of included studies on 19 December 2019 using Web of Science. SL conducted a search of grey literature using OpenGrey on 9 January 2020 (www.opengrey.eu), and we scanned reference lists of systematic reviews that we identified in the database searches.

Data collection and analysis

Two review authors (PB and SL) independently selected studies and extracted data from the new included study. We compared decisions at each stage. In cases of disagreement, we reassessed the respective studies to reach consensus.

Selection of studies

We used reference management software to collate the results of searches and to remove duplicates ([Endnote](#)). We used Covidence software to screen results of the search of titles and abstracts and to identify potentially relevant studies ([Covidence 2019](#)). We sourced the full texts of all potentially relevant studies and considered whether they met the inclusion criteria (see [Criteria for considering studies for this review](#)).

We recorded the number of papers retrieved at each stage and reported this information using a PRISMA flow chart.

Data extraction and management

We adapted a template data extraction form in Covidence to collect information and outcome data from studies. We requested additional information from study authors as required, and planned to include this information in the data extraction forms.

We collected the following information.

- Methods: type of study design; setting; dates of study; funding sources; and study author declarations of interest.
- Participants: number randomised to each group; number of losses in each group (with reasons for loss); number analysed in each group; baseline characteristics (age, gender, mechanism of injury, associated extracranial injuries, duration from injury to presentation at a hospital).
- Interventions: details of intervention and comparison (for drug therapy: route of drug; for equipment: physical cooling method); lowest body temperature attained; duration of intervention; the time between the onset of the initial injury and commencement of cooling therapy; site of temperature measurement.
- Outcomes: data for all reported outcomes, to include study author definitions, measurement scales, and time points.

For each study, we also assessed whether an intention-to-treat analysis was used according to the following criteria.

- Yes: authors specifically reported that they undertook intention-to-treat analysis, and we confirmed this on study assessment.
- Yes: not stated, but confirmed on study assessment.
- No: not reported and lack of intention-to-treat analysis confirmed on study assessment (participants who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study, or were not included because of protocol violation).
- No: stated, but not confirmed on study assessment.
- Not stated.

Assessment of risk of bias in included studies

We assessed study quality, study limitations, and the extent of potential bias using the Cochrane 'Risk of bias' tool (Higgins 2011). We considered the following domains.

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessors (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other risks of bias

For each domain, two review authors (PB and SL) judged whether study authors made sufficient attempts to minimise bias in their study design. For performance bias, we considered there to be no blinding if the treatment group could be identified in more than 20% of participants because of the side effects of treatment. For each domain, we made judgements of high, low, or unclear risk

of bias. We recorded this in 'Risk of bias' tables and presented a summary 'Risk of bias' figure.

Measures of treatment effect

We intended to collect only data that were reported dichotomously. In future updates of this review, for the primary outcome, we will collect the number of people who had a score between one and three on the GOS (to indicate death or disability). For the secondary outcomes, we will collect the number of people that died, had serious intracranial haemorrhage, extracranial haemorrhage, abnormal intracranial pressure, or pneumonia or other serious infection.

We reported risk ratios (RR) with 95% confidence intervals (CIs) to compare groups. For outcomes with data from single studies only, we used the calculator in RevMan 5.3 to calculate RRs using the Mantel-Haenszel method (Review Manager 2014).

Unit of analysis issues

In the event of an included study having more than one eligible intervention group within the same comparison (for example, two types of pharmacological agent), we planned to combine the data in the intervention arms. We did not plan to use subgroup analysis according to types of pharmacological interventions or types of physical interventions, and therefore we did not need to consider risk of double counting participants within the same analysis.

Dealing with missing data

We attempted to contact study authors for more information on missing data. If we had identified an eligible study that provided no useable data for analysis, we had planned to include the study and to describe its methods in the 'Characteristics of included studies' table.

Assessment of heterogeneity

We planned to consider clinical homogeneity of the included studies by comparing similarities between study designs, participants, interventions, and methods of outcome measurement using the data we had collected from the full-text reports (see Data collection and analysis). For studies we considered to be clinically homogeneous, we planned to test statistical heterogeneity using the Chi² test and I² statistic. We would have assumed statistical heterogeneity with a Chi² P value less than 0.10, and considered an I² value above 50% to indicate moderate statistical heterogeneity.

Assessment of reporting biases

If we had included 10 or more studies in an analysis, we had planned to assess potential reporting bias using funnel plots and linear regression.

Data synthesis

We planned to present a statistical summary of treatment effects for outcomes in each comparison group (pharmacological interventions and physical interventions) in the absence of significant clinical or methodological heterogeneity, using RevMan 5 to perform meta-analysis (Review Manager 2014). We planned to express these as RRs with 95% CIs, using the Mantel-Haenszel method with a random-effects model.

We planned to consider imprecision in the results of analyses by assessing the CI around an effects measure; a wide CI would suggest a higher level of imprecision in our results. A small number of studies may also reduce precision ([Guyatt 2011](#)).

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analysis because we found insufficient studies in each comparison group; at least 10 studies would have enabled meaningful subgroup analysis ([Deeks 2019](#)). If we had found sufficient studies, we planned to evaluate possible sources of heterogeneity with the following subgroups.

- Adults (≥ 18 years old) versus children
- Temperature reduction achieved (35°C to $\leq 36^{\circ}\text{C}$ versus placebo and $> 36^{\circ}\text{C}$ to 37.5°C versus placebo)
- Duration of temperature reduction

Sensitivity analysis

Previously, we did not report plans for sensitivity analysis ([Saxena 2014](#)), and it was not possible to conduct sensitivity analysis in this update because we found too few studies. In future updates, we will use sensitivity analysis to explore the effects of risk of bias in the included studies, and the effects of the model used in meta-analysis. We will compare the effects from the following sensitivity analyses with the effects from the primary analyses:

- we will exclude studies that we judge to have a high or unclear risk of selection bias;
- we will use the alternative effects model in analysis (i.e. a fixed-effect model or a random-effects model).

'Summary of findings' table and GRADE

Two review authors (PB and SL) used the GRADE system to assess the certainty of the body of evidence and construct a 'Summary of findings' table associated with the following outcomes ([Guyatt 2008](#)).

- Poor outcome at the end of follow-up
- Death from all causes during the follow-up period

- Further serious intracranial haemorrhage
- Extracranial haemorrhage
- Abnormal intracranial pressure
- Pneumonia or other serious infections

The GRADE approach appraises the certainty of a body of evidence based on the extent to which we can be confident that an estimate of effect or association reflects the item being assessed. Evaluation of the certainty of a body of evidence considers within-study risk of bias, directness of the evidence, heterogeneity of the data, precision of the effect estimates, and risk of publication bias. For the primary outcome (poor outcome), we considered an information size to determine precision of the effect estimate; with a conventional dichotomous analysis of the GOS that compares the proportions of participants with an unfavourable outcome in the two groups (normothermia versus control), a minimum of 716 people need to be randomised in order to have 90% power at the 5% significance level (2-sided) to detect an absolute reduction of 12% (60% reducing to 48%) of an unfavourable outcome.

Had studies been available, we planned to construct 'Summary of findings' tables using GRADEpro GDT software for the following comparisons in this review ([grade.pro.org](#)).

- Pharmacological interventions
- Physical interventions

RESULTS

Description of studies

Results of the search

After the removal of duplicates from the search results, we screened 827 titles and abstracts for this update, which included forward- and backward-citation searches, clinical trials registers and grey literature. We sourced 17 full-text reports to assess eligibility. Examination of their full texts revealed nine excluded studies (11 reports), one study that is awaiting classification (one report), four ongoing studies (four reports), and one study that we included in the review (one report). A summary of this process is provided in the PRISMA flow chart ([Figure 1](#)).

Figure 1. Study flow diagram. Updated database search conducted 28 November 2019.

Figure 1. (Continued)

Included studies

See [Characteristics of included studies](#).

We included one RCT with 41 participants ([Saxena 2015](#)).

[Saxena 2015](#) included adult participants who had been admitted to the intensive care units within 72 hours of non-penetrating TBI and required mechanical ventilation. This study was conducted at two university-affiliated trauma centres in Australia; investigators received funding from sources which we believe were independent (combined funding from a professional organisation and research association). Study authors evaluated a pharmacological therapy; they compared the effects of 1 g paracetamol versus saline (as a placebo) given intravenously every four hours for 72 hours.

We found no studies that evaluated physical interventions.

Excluded studies

We excluded nine articles (with 11 reports) following assessment of the full texts ([Figure 1](#)). We excluded five RCTs because cooling of participants with TBI was lower than 35 °C ([Feng 2017](#); [Idris 2014](#); [Jing 2014](#); [Sinha 2017](#)), or crossed the temperature threshold eligible for this review ([Prasetyo 2018](#)). We excluded an RCT of temperature management (currently only published as a protocol) because it did not include participants with TBI ([Young 2017](#)), and a study of temperature management of people with TBI because it was not an RCT ([Sadaka 2013](#)). We also excluded two articles which were commentaries on non-eligible studies ([Ahmad 2016](#); [Pines 2016](#)). See [Characteristics of excluded studies](#).

Ongoing studies

See [Characteristics of ongoing studies](#).

We identified four ongoing trials with an estimated enrolment of 1368 participants ([ACTRN12615001119583](#); [NCT02996266](#); [NCT03496545](#); [NCT03648021](#)). Two studies are evaluating a physical cooling device ([ACTRN12615001119583](#); [NCT02996266](#)), however, as one of these trials includes a mixed brain injury population, we will only include the final published study in future versions of the review if data are reported separately for participants with TBI ([NCT02996266](#)). Similarly, we will only include the two studies evaluating pharmacological therapies (bromocriptine, and paracetamol) if they report data separately for participants with TBI ([NCT03496545](#); [NCT03648021](#)); these studies currently do not indicate that they will collect outcome data that are relevant to this review.

Studies awaiting classification

See [Characteristics of studies awaiting classification](#).

We found one study, published only as an abstract, which reported insufficient information to describe the intervention and control ([Sadaka 2015](#)). This small study, with 12 participants, compared advanced fever control (using a surface cooling device) with conventional fever control.

Risk of bias in included studies

We judged [Saxena 2015](#) to be at low risk of selection bias (sequence generation and allocation concealment), performance and detection bias, attrition bias, and other bias. [Saxena 2015](#) was registered prospectively with a clinical trials register. However, we noted that the published study reported data for mortality and this outcome was not listed on the clinical trials register. We therefore judged this study to be at high risk of reporting bias; this judgement is specific to data for mortality. Our 'Risk of bias' judgements are summarised in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for the included study.

Effects of interventions

See: [Summary of findings 1](#) Cooling to 35 °C to 37.5 °C for traumatic brain injury: pharmacological interventions

Pharmacological interventions

Primary outcome

Poor outcome at the end of follow-up

We found no studies that reported data for this outcome.

Death from all causes at the end of follow-up

[Saxena 2015](#) reported three deaths in 21 participants who were given paracetamol, and one death in 20 control group participants. The follow-up period in this study was 28 days following injury. We could not be certain whether using paracetamol as a cooling therapy reduced or increased mortality (RR 2.86, 95% CI 0.32 to 25.24; 1 study, 41 participants; very low-certainty evidence). We used GRADE to downgrade the certainty of the evidence by three levels; one level for study limitations owing to high risk of selective reporting bias, and two levels owing to imprecision because the

evidence was from a single study with a very small sample size. See [Summary of findings 1](#).

Further serious intracranial haemorrhage

We found no studies that reported data for this outcome.

Extracranial haemorrhage

We found no studies that reported data for this outcome.

Abnormal intracranial pressure

We found no studies that reported data for this outcome.

Pneumonia or other serious infections

We found no studies that reported data for this outcome.

Physical interventions

We found no studies that assessed physical interventions to reduce body temperature to 35 °C to 37.5 °C.

DISCUSSION

Summary of main results

We identified only one eligible study to include in the review. We also found one very small study which is awaiting classification; this study is published only as an abstract, with insufficient details about the intervention and comparison therapies to allow a decision about inclusion. Four studies are ongoing.

The small included study compared 1 g of intravenously administered paracetamol with a placebo. This was administered for 72 hours to people in the intensive care unit who had sustained a non-penetrating TBI in the previous 72 hours. We could not be sure whether paracetamol reduced or increased mortality within 28 days of injury because the certainty of the evidence was very low. The study reported no other outcomes relevant to this review.

We identified no other evidence to support or refute the use of any type of pharmacological or physical interventions used to reduce body temperature to 35 °C to 37.5 °C to improve poor outcomes (death or dependency), further serious intracranial haemorrhage, extracranial haemorrhage, abnormal intracranial pressure, pneumonia or other serious infections.

Overall completeness and applicability of evidence

The single included study randomised only 41 participants and its criteria were applicable to our review question - all participants had a TBI and were treated with an appropriate pharmacological intervention. However, any effect could only be applicable to adults under 65 years of age who were treated with paracetamol within 72 hours of injury, and not to other age groups eligible in this review, other types of pharmacological interventions or any type of physical intervention. The included study did not measure most outcomes relevant to this review, and the number of participants was too low to enable confident evaluation of the effect of this intervention on mortality in this population.

Quality of the evidence

We used GRADE to assess the certainty of the evidence for our secondary outcome of death at the end of follow-up. Because the evidence was from one small study, we downgraded the certainty

by two levels for imprecision. We also noted a high risk of selective reporting bias for this outcome, so we also downgraded by one level for study limitations.

Potential biases in the review process

This review is an update of a previous version in which no studies were identified ([Saxena 2014](#)). Before beginning the update, the lead study author informed the Cochrane Injuries Group that the updated review would include a study for which he was the principle investigator. Therefore, new review authors (PB and SL) conducted the update. These new authors conducted a thorough search and independently assessed study eligibility, extracted data, and assessed risk of bias in the included study before reaching consensus through discussion with one another. The previous author team were involved only in evaluation of the final draft of this review.

During the updating process, we made minor changes to the review to meet current Cochrane methodological standards. We do not believe that these changes introduced bias into the current version of the review.

Agreements and disagreements with other studies or reviews

We are not aware of any systematic reviews or other study designs that evaluated cooling therapies to reduce body temperature to 35 °C to 37.5 °C specifically for TBI. We are therefore unable to compare our findings with those of other researchers.

AUTHORS' CONCLUSIONS

Implications for practice

Only one small study contributed evidence for mortality in this review, and our certainty in the treatment effect is very low. As such, we believe that the estimated study effect for mortality is likely to be very different from the true result. This uncertainty is largely driven by limited research into cooling therapies that aim to reduce body temperature to 35 °C to 37.5 °C in people with traumatic brain injury (TBI). We found no evidence relating to the effect of interventions on our primary outcome of whether people have a poor outcome (defined as death or dependency on the Glasgow Outcome Scale (GOS)), or for our other secondary outcomes, which included further serious intracranial haemorrhage, extracranial haemorrhage, abnormal intracranial pressure, and pneumonia or other serious infections. The evidence was applicable only to adults, and assessed only one type of pharmacological intervention (paracetamol). We found no studies on physical interventions. Further research that evaluates either pharmacological or physical interventions may increase certainty in this field.

Implications for research

Randomised controlled trials of cooling therapies that aim to reduce body temperature to 35 °C to 37.5 °C after TBI are required to evaluate their effect on outcomes; research is needed for both drug interventions and physical interventions. Currently, additional evidence is required for all existing outcomes in the review, which are: poor outcome (using the GOS), death from all causes, further serious intracranial haemorrhage, extracranial haemorrhage, abnormal intracranial pressure, and pneumonia or other serious infections. However, this review does not sufficiently

explore outcomes that may be important to the person who is receiving the treatment. Pharmacological therapies may have effects such as pain on injection, or nausea or vomiting, and physical therapies may cause discomfort or distress. The single study included in this version of the review did not report any of these outcomes. We propose that future review updates expand the existing outcomes to also include outcomes that are important to people with TBI who may receive relevant interventions. Ongoing or future research in this field would benefit from consideration of such outcomes.

ACKNOWLEDGEMENTS

The authors would like to thank the Cochrane Injuries Group Editorial Base, the Cochrane Renal Group and the authors of the previous Cochrane Reviews 'Therapeutic hypothermia for head

injury' ([Alderson 2004](#); [Lewis 2017](#); [Sydenham 2009](#)), and 'Cooling therapy for acute stroke' ([Den Hertog 2009](#)). We are grateful to Dr Doris Lam for her help in translating literature from Chinese journals in previous versions of the review.

We would also like to thank the peer reviewers, Luis Rafael Moscote-Salazar, and Danial Sayyad and consumer referee, Jo Weldon, for their input.

This project was supported by the UK National Institute for Health Research (NIHR), through Cochrane Infrastructure funding to the Cochrane Injuries Group. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Saxena 2015

Study characteristics

Methods	RCT, parallel design
Participants	<p>Total number of randomised participants: 41</p> <p>Inclusion criteria: 18 to 65 years of age; non-penetrating TBI, defined by a brain injury due to mechanical forces and the presence of haemorrhage, contusion, swelling, compression of basal cisterns or herniation on cerebral CT scan; requirement for mechanical ventilation; serum alanine transferase level < 100 IU/L</p> <p>Exclusion criteria: use of any pharmacological or physical intervention that could modify temperature within the previous 6 hours or clinician intent to modify body temperature using any pharmacological or physical intervention; body temperature < 36 °C or > 38.9 °C; prespecified risk factors for paracetamol toxicity; TBI not expected to require intensive care management for 72 hours after randomisation; GCS of 3 with fixed, dilated pupils, or moribund patient expected to die within 24 hours; confirmed or suspected pregnancy</p> <p>Baseline characteristics:</p> <p>Study authors stated, "There was no difference in baseline characteristics between the two groups".</p> <p>Intervention group (1 g paracetamol IV)</p> <ul style="list-style-type: none"> Age, mean (SD): 33 (± 16) years Gender, M:F: 18:3 Mechanism of injury: motor vehicle = 11; fall = 4; other = 6 Major extracranial injury: 5 Time from injury to ED admission, median (IQR): 1:47 (0.50 to 3.25) hours GCS scores, median (IQR): 6 (3 to 7) APACHE II scores, mean (SD): 18 (± 4)

Saxena 2015 (Continued)

Control group (saline IV)

- Age, mean (SD): 33 ($\pm$ 18) years
- Gender, M:F: 15:5
- Mechanism of injury, n: motor vehicle = 11; fall = 7; other = 2
- Major extracranial injury, n: 8
- Time from injury to ED admission, median (IQR): 2:42 (0.59 to 3.33) hours
- GCS scores, median (IQR): 7 (3 to 9)
- APACHE II scores, mean (SD): 18 ($\pm$ 4)

Country: Australia

Setting: ICUs in 2 centres

Interventions	<p>Intervention group (1 g paracetamol IV)</p> <ul style="list-style-type: none"> • Number randomised = 21; withdrawal of 1 participant by the treating clinician; number analysed = 21 (ITT done) • Details: 1 g paracetamol IV over 30 minutes, every 4 hours for 72 hours. In each dose: mannitol 3.85 g, cysteine hydrochloride, sodium phosphate dihydrate, sodium hydroxide, hydrochloric acid (study authors reported only the amount of mannitol in the composition of paracetamol). No other pharmacological intervention (including NSAIDs). Physical cooling was only used if temperature $> 38^{\circ}\text{C}$ or ICP > 20 mmHg. • Other treatments given: 14/21 phenytoin; 13/20 ICP monitoring • Site of temperature monitoring: bladder, unless urethral injury/renal failure, in which case tympanic, axillary and nasopharyngeal measurements were taken and adjusted accordingly. • Time between injury and start of cooling: not reported • Any neurological deterioration after starting of cooling: not reported • Duration of physical cooling, mean (SD): 2.2 ($\pm$ 0.7) hours per day <p>Control group (saline IV)</p> <ul style="list-style-type: none"> • Number randomised = 20; no losses; number analysed = 20 (ITT done) • Details: same as the intervention group but IV paracetamol replaced by 100 mL 0.9% saline IV • Other treatments given: 19/20 phenytoin; 15/20 ICP monitoring; physical cooling with the same criteria as for the intervention group • Site of temperature monitoring: bladder, unless urethral injury/renal failure, in which case tympanic, axillary and nasopharyngeal measurements were taken and adjusted accordingly • Time between injury and start of cooling: not reported • Any neurological deterioration after starting of cooling: not reported • Duration of physical cooling, mean (SD): 3.8 ($\pm$ 1.2) hours per day
Outcomes	<p>Outcomes reported by study authors: difference in mean core temperature, number of hours of physical cooling, MAP, and ICP; ICU and hospital length of stay; mortality (at 28 days); hypotension during treatment; cerebral hypoperfusion; hepatic abnormalities within 7 days of randomisation.</p> <p>Outcomes relevant to the review: mortality</p>
Notes	<p>Funding and declarations of interest: supported by a project grant from the Australia and New Zealand College of Anaesthetists and the St George Medical Research Foundation. The funders had no role in the study conduct, in the interpretation of the findings or presentation of the study report. The study authors declared they had no competing interests</p> <p>Study dates: November 2010 to December 2013</p>
Risk of bias	
Bias	Authors' judgement Support for judgement

Saxena 2015 (Continued)

Random sequence generation (selection bias)	Low risk	Use of computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Randomisation was conducted by individuals not involved in the treatment of participants, and preparation of solutions was done externally.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "At each study site, independent individuals who were not involved in the study or clinical activities, prepared study solutions according to randomisation codes; the study solutions were blinded, by the use of an opaque shroud to conceal differences in product packaging, although the two solutions were macroscopically indistinguishable." Quote: "Participants, healthcare providers, data collectors, outcome adjudicators, data analysts and investigators were all unaware of treatment allocation during the conduct of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants, healthcare providers, data collectors, outcome adjudicators, data analysts and investigators were all unaware of treatment allocation during the conduct of the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant withdrawn from study in the intervention group. Data analysed as ITT.
Selective reporting (reporting bias)	High risk	Prospective clinical trials registration (ACTRN12609000444280 and NCT01231139). We noted a discrepancy between the clinical trials register documents and the final published report. The published study reports outcome data for 28 day mortality; this outcome is not listed in the clinical trials register documents and we judged this to indicate a risk of selective reporting bias because of over-reporting.
Other bias	Low risk	We identified no other sources of bias.

APACHE II: Acute Physiology and Chronic Health Evaluation II; **CT:** computed tomography; **ED:** emergency department; **GCS:** Glasgow Coma Scale; **ICP:** intracranial pressure; **ICU:** intensive care unit; **IQR:** interquartile range; **ITT:** intention to treat; **IV:** intravenous(ly); **MAP:** mean arterial pressure; **M:F:** male:female; **NSAIDs:** nonsteroidal anti-inflammatory drugs; **RCT:** randomised controlled trial; **SD:** standard deviation; **TBI:** traumatic brain injury

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahmad 2016	We excluded this publication because it is a commentary article, which is not eligible.
Feng 2017	RCT: participants with severe TBI (GCS 3 to 8), cooling to target 50% to 60% of rest metabolic rate versus hypothermia 32 °C to 35 °C. Excluded because this intervention is not eligible.
Idris 2014	RCT: participants with TBI (GCS 6 and 7) who required decompressive craniectomy. Participants' brains were cooled by irrigation with cold Hartmann solution to maintain temperatures of 20 °C to 29 °C versus 30 °C to 36 °C. Excluded because this intervention is not eligible.
Jing 2014	RCT: participants with diffuse axonal injury, intervention was cooling to normothermia or hypothermia (32 °C to 35 °C). Excluded because this temperature range is < 35 °C, and therefore too low.
Pines 2016	We excluded this publication because it is a commentary article, which is not eligible.

Study	Reason for exclusion
Prasetyo 2018	RCT: participants with severe TBI (FOUR score < 7), with or without hypothermia (34 °C to 36 °C). Excluded because this intervention includes temperatures < 35 °C, which is outside our specified temperature range.
Sadaka 2015	This study gave boluses of 4 °C normal saline (varying volumes) in addition to paracetamol, ibuprofen and a cooling blanket to people with TBI to induce hypothermia. We excluded this study on the basis of study design; the method of allocation was not stated, and study authors implied that it is not an RCT.
Sinha 2017	RCT: adults with acute, severe TBI. Participants randomised to placebo, hypothermia (32 °C to 33 °C), progesterone, or progesterone + hypothermia (32 °C to 33 °C). Excluded as this temperature is < 35 °C.
Young 2017	This is a protocol for an RCT. Excluded because the participants did not have TBI.

FOUR: full outline of unresponsiveness; **GCS:** Glasgow Coma Scale; **RCT:** randomised controlled trial; **TBI:** traumatic brain injury

Characteristics of studies awaiting classification [ordered by study ID]

Sadaka 2013

Methods	RCT, parallel design
Participants	<p>Total number of randomised participants: 12</p> <p>Inclusion criteria: severe TBI (GCS < 9)</p> <p>Exclusion criteria: unknown</p> <p>Baseline characteristics:</p> <p>Baseline characteristics were not reported. Study authors stated, "There was no difference in the 2 groups regarding GCS, vasopressors, or sedation"</p> <p>Country: USA</p> <p>Setting: single centre</p>
Interventions	<p>Intervention group (advanced fever control)</p> <ul style="list-style-type: none"> Number randomised = 8; losses not reported, we have assumed 0; number analysed = 8 Details: surface cooling device to 37 °C for 96 hours <p>Control group (conventional fever control)</p> <ul style="list-style-type: none"> Number randomised = 4; losses not reported, we have assumed 0; number analysed = 4 Details: not described.
Outcomes	<p>Outcomes measured/reported by study authors: fever burden (time and extent > 37 °C); CT scan progression; mortality; discharge location; good GOS (score 4 to 5); number of times BSAS score > 0</p> <p>Outcomes relevant to the review: mortality, poor outcome</p>
Notes	<p>Funding/declarations of interest: no financial support. Conflicts of interest not reported.</p> <p>Study dates: June 2011 to May 2013</p> <p>Note: study was published as an abstract only, with limited data. We attempted to contact the study authors via email for additional information, but received no reply. The abstract included in-</p>

Sadaka 2013 (Continued)

sufficient information about the method of surface cooling in the intervention group and the methods used for conventional fever control. We await publication of the full study report, or sufficiently detailed information from the study authors.

BSAS: bedside shivering assessment score; **CT:** computed tomography; **GCS:** Glasgow Coma Scale; **GOS:** Glasgow Outcome Score; **RCT:** randomised controlled trial; **TBI:** traumatic brain injury

Characteristics of ongoing studies [ordered by study ID]

ACTRN12615001119583

Study name	Target temperature management for traumatic brain injury: a feasibility study of pyrexia control
Methods	Pilot RCT, parallel design
Participants	<p>Estimated number of participants: 50</p> <p>Inclusion criteria: > 16 years of age with blunt trauma and a clinical diagnosis of TBI (blunt head trauma, GCS < 13 prior to sedation, CT scan of head consistent with TBI); requiring invasive mechanical ventilation (predicted requirement for > 1 day); screened and randomised within 24 hours of injury</p> <p>Exclusion criteria: treating physician intends to control temperature or induce hypothermia as part of the management plan, or both; treating clinician deems participation is not in the patient's best interests; drug or alcohol intoxication is likely to be the predominant cause of coma; cardiac arrest at scene of injury; spinal cord injury with confirmed neurological deficit; pregnancy; disability prior to injury, defined by a score of 4 or less as assessed by the extended GOS; death deemed to be imminent or inevitable, or a treatment limitation order is in place; underlying process or comorbidity making 180 day survival unlikely</p>
Interventions	Choice of intervention (physical cooling devices) at the discretion of treating clinician versus standard care. Intervention to be used for at least 72 hours in order to control temperature at 36 °C
Outcomes	<p>All outcomes reported: mean temperature difference between intervention and control groups; duration of mechanical ventilation; ICP (for participants receiving ICP monitoring as part of standard care).</p> <p>Outcomes relevant to this review: ICP</p>
Starting date	1 February 2016
Contact information	Dr Manoj Saxena; msaxena@georgeinstitute.org.au
Notes	Study currently has provisional registration on the clinical trials register.

NCT02996266

Study name	Impact of fever prevention in brain injured patients (INTREPID)
Methods	RCT, parallel design
Participants	<p>Estimated number of participants: 1178</p> <p>Inclusion criteria: admitted with a primary neurological diagnosis of ischaemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage; prior to onset of acute symptoms, participant was considered functionally independent (mRS 0 to 2); meets disease-specific criteria</p>

NCT02996266 (Continued)

	<p>Exclusion criteria: fever ($\geq 38^{\circ}\text{C}$) prior to study enrolment; pre-existing neurological, psychiatric, or other condition that would confound neurological assessment or would make it difficult to assess neurologic or functional outcome, or both, accurately; premorbid condition with poor likelihood of survival to 6 months; pre-morbid mRS ≥ 3; diagnosed with brain death; undergoing therapeutic hypothermia therapy; sustained neurological injury expected to be catastrophic with little chance of recovery; skin condition for which the use of the Arctic Gel Pads is contraindicated (i.e. skin that has signs of ulceration, burns, hives, or rash); poor skin integrity or poor tissue perfusion; participation in a concurrent investigational or interventional study (medical device or drug)</p>
Interventions	Participants receive induced normothermia with surface targeted physical cooling device (Arctic Sun 5000 Temperature Management System) versus standard care
Outcomes	<p>All outcomes reported: fever burden; mRS (3, 6 and 12 months), NIH Stroke Scale, Barthel Index, GOS, Montreal Cognitive Assessment (all for 3 and 6 month follow-up); adverse events; infection rate; incidence of shivering; length of hospital stay; mortality.</p> <p>Outcomes relevant to this review: GOS (6 months); adverse events; infection rate; mortality</p>
Starting date	January 2017
Contact information	Peter Fayek; peter.fayek@bd.com
Notes	We will consider inclusion in this review, if study authors report data separately for participants with TBI.

NCT03496545

Study name	Efficacy of bromocriptine on febrile adults with acute neurologic diseases
Methods	Pilot RCT, parallel design
Participants	<p>Estimated number of participants: 40</p> <p>Inclusion criteria: ≥ 18 years of age; weight ≥ 40 kg; one reading of body temperature $\geq 38.3^{\circ}\text{C}$; diagnosis of subarachnoid haemorrhage, intracerebral haemorrhage, TBI, subdural haematoma, or ischaemic stroke; admission to the ICU</p>
Interventions	Bromocriptine + paracetamol versus paracetamol
Outcomes	<p>All outcomes reported: temperature burden; incidence of bromocriptine-induced adverse events (symptomatic hypotension, nausea and headache); total time that temperature is $\geq 38.3^{\circ}\text{C}$; total time to first temperature $< 37.5^{\circ}\text{C}$</p> <p>Outcomes relevant to this review: none</p>
Starting date	30 November 2018
Contact information	<p>Judy H Ch'ang; judy.chang@ucsf.edu</p> <p>Anthony S Kim; anthony.kim@ucsf.edu</p>
Notes	Only a subpopulation of participants with TBI is eligible for inclusion in this review. We will only include this study if data are reported separately for participants with TBI. We note that currently outcomes relevant to the review are not included in the clinical trials register.

NCT03648021

Study name	The effect of paracetamol on brain temperature (NEUROTHERM)
Methods	RCT, parallel design
Participants	<p>Estimated number of participants: 100</p> <p>Inclusion criteria: ≥ 18 years of age; hospitalised in neuro-critical care for arachnoid haemorrhage, intraparenchymatous haematoma; stroke, acute brain injury; postoperative complication of neurosurgery or neuroradiology; sedation and mechanical ventilation planned for > 2 days; monitoring of intracranial temperature and ICP by intraparenchymal sensor; brain temperature > 38.5 °C for > 30 minutes</p> <p>Exclusion criteria: known hypersensitivity to paracetamol or mannitol; severe hepatocellular insufficiency;</p> <p>pharmacological intervention (administration of corticosteroids, NSAIDs or paracetamol) or physical intervention (external cooling technique) that may influence temperature in the last 6 hours; pregnant or breastfeeding women; previous participation in this study</p>
Interventions	Paracetamol versus saline (placebo)
Outcomes	<p>All outcomes reported: temperature between start and 6 hours</p> <p>Outcomes relevant to this review: none</p>
Starting date	10 April 2018
Contact information	Amélie Yavchitz. ayavchitz@for.paris
Notes	Only a subpopulation of participants with TBI may be eligible for inclusion in this review. We will only include this study if data are reported separately for participants with TBI. We note that currently outcomes relevant to the review are not included in the clinical trials register.

CT: computed tomography; **GCS:** Glasgow Coma Scale; **GOS:** Glasgow Outcome Score; **ICP:** intracranial pressure; **ICU:** intensive care unit; **mRS:** modified Rankin Scale; **NIH:** National Institutes for Health; **NSAIDs:** nonsteroidal anti-inflammatory drugs; **RCT:** randomised controlled trial; **TBI:** traumatic brain injury

APPENDICES

Appendix 1. Searches for previous versions

National Research Register 2007, issue 3

- #1 MeSH descriptor Hypothermia explode all trees
- #2 MeSH descriptor Hypothermia, Induced explode all trees
- #3 MeSH descriptor Cryotherapy explode all trees
- #4 hypotherm* or cryotherap*
- #5 (cool* or cold) near3 (therap* or device* or equipment)
- #6 (temperature near3 reduc*)
- #7 intravenous near3 (cold or cool*)
- #8 fluid* or catheter*
- #9 (#7 AND #8)
- #10 (cool* or cold*) near3 (blanket* or neck collar* or helmet* or hood*)
- #11 ice-water lavage
- #12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 OR #10 OR #11)
- #13 MeSH descriptor Analgesics, Non-Narcotic explode all trees
- #14 analgesic* near3 (non-narcotic* or non-opioid*)
- #15 MeSH descriptor Acetaminophen explode all trees

#16 antipyretic*

#17 Aspirin or Meclofenamate sodium or Niflumic acid or Tiaprofenic acid or Tolfenamic acid or Acemetacine or Naproxen or Diclofenac or Etodolac or Fentiazac or Etofenamato or Fenbufen or Fentiazac or Nimesulid or Flurbiprofen or Ibuprofen or Indomethacin or Sulindac or ketoprofen or Lonazolac or Piroxicam or Tenoxicam or Proglumetacina or acetaminophen or paracetamol or acetamidophenol or hydroxyacetanilide or apap or acamol or acephen or acetaco or acetaminophen or algotropyl or anacin-3 or datril or n-4-hydroxyphenyl acetanilide or n-acetyl-p-aminophenol or panadol or Tylenol or p-acetamidophenol

#18 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees

#19 (analgesic* or non-steroidal) near3 (anti-inflammatory*)

#20 NSAID* or anti-rheumatic* or aspirin-like

#21 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)

#22 MeSH descriptor Body Temperature explode all trees

#23 MeSH descriptor Body Temperature Regulation explode all trees

#24 body near3 temperature

#25 body near3 (cool* or cold*)

#26 (#22 OR #23 OR #24 OR #25)

#27 (#21 AND #26)

#28 MeSH descriptor Craniocerebral Trauma explode all trees

#29 MeSH descriptor Cerebrovascular Trauma explode all trees

#30 MeSH descriptor Brain Edema explode all trees

#31 MeSH descriptor Glasgow Coma Scale explode all trees

#32 MeSH descriptor Glasgow Outcome Scale explode all trees

#33 MeSH descriptor Unconsciousness explode all trees

#34 glasgow near3 scale*

#35 Unconscious* or coma* or concuss* or 'persistent vegetative state'

#36 Rancho Los Amigos Scale

#37 (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*)

#38 Diffuse axonal injur*

#39 (#37 OR #38)

#40 (#32 OR #33 OR #34 OR #35 OR #36)

#41 (#39 AND #40)

#42 (#28 OR #29 OR #30 OR #39 OR #41)

#43 (#27 AND #42)

ZETOC (April 2008)

head injur* cool*

OR

brain injur* cool*

OR

head injur* mild hypotherm*

OR

brain injur* mild hypotherm*

OR

head injur* modest hypotherm*

OR

brain injur* modest hypotherm*

Appendix 2. Organisations contacted

For the version of this review published in 2014, we contacted the following pharmaceutical companies on 9 December 2013:

- Reckitt Benckiser (aspirin and ibuprofen);
- Merck Sharpe Dome (indomethacin and sulindac);
- Novartis (diclofenac);
- Mylan (meclofenamate sodium);
- Cayman (neflumic acid);
- Sanofi-Aventis (ketoprofen and tiaprofenic acid);
- Galen (tolfenimic acid);
- Pharma 24 (acemetacine);
- Roche (naproxen and tenoxicam);
- Wyeth-Lederle (etodolac, fentiazac and fenbufen);

- Helsinn healthcare (nimesulide);
- Pfizer (flurbiprofen and piroxicam);
- Rotta (proglumetacin);
- Johnson and Johnson (acetaminophan); and,
- Bristol-Myers-Squibb (paracetamol).

We also contacted the following manufacturers of cooling equipment on 9 December 2013:

- Coolgard Cool line catheter (Alsus CA);
- Tyco healthcare (Warmtouch 5800);
- Gaymar USA (MTA 4702);
- Arizant (Polar Air Model 600 Air Cooling System) Cincinnati, Ohio (subzero); and,
- Medivance (arctic sun temperature management system).

Appendix 3. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

```
#1MeSH descriptor: [Hypothermia] explode all trees
#2MeSH descriptor: [Hypothermia, Induced] explode all trees
#3MeSH descriptor: [Cryotherapy] explode all trees
#4hypotherm* or cryotherap*:ti,ab,kw (Word variations have been searched)
#5(cool* or cold) near/3 (therap* or device* or equipment):ti,ab,kw (Word variations have been searched)
#6(temperature near/3 reduc*):ti,ab,kw (Word variations have been searched)
#7intravenous near/3 (cold or cool*):ti,ab,kw (Word variations have been searched)
#8fluid* or catheter*:ti,ab,kw (Word variations have been searched)
#9#7 and #8
#10(cool* or cold*) near/3 (blanket* or neck collar* or helmet* or hood*):ti,ab,kw (Word variations have been searched)
#11ice-water lavage:ti,ab,kw (Word variations have been searched)
#12(#1 or #2 or #3 or #4 or #5 or #6 or #9 or #10 or #11)
#13MeSH descriptor: [Analgesics, Non-Narcotic] explode all trees
#14analgesic* near/3 (non-narcotic* or non-opioid*):ti,ab,kw (Word variations have been searched)
#15MeSH descriptor: [Acetaminophen] explode all trees
#16antipyretic*:ti,ab,kw (Word variations have been searched)
#17Aspirin or Meclofenamate sodium or Niflumic acid or Tiaprofenic acid or Tolfenamic acid or Acemetacine or Naproxen or Diclofenac or Etodolac or Fentiazac or Etofenamato or Fenbufen or Fentiazac or Nimesulid or Flurbiprofen or Ibuprofen or Indomethacin or Sulindac or ketoprofen or Lonazolac or Piroxicam or Tenoxicam or Proglumetacina or acetaminophen or paracetamol or acetamidophenol or hydroxyacetanilide or apap or acamol or acephen or acetaco or acetaminophen or algotropyl or anacin-3 or datril or n-4-hydroxyphenyl acetanilide or n-acetyl-p-aminophenol or panadol or Tylenol or p-acetamidophenol:ti,ab,kw (Word variations have been searched)
#18MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#19(analgesic* or non-steroidal) near/3 (anti-inflammator*):ti,ab,kw (Word variations have been searched)
#20NSAID* or anti-rheumatic* or aspirin-like:ti,ab,kw (Word variations have been searched)
#21(#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#22MeSH descriptor: [Body Temperature] explode all trees
#23MeSH descriptor: [Body Temperature Regulation] explode all trees
#24body near/3 temperature:ti,ab,kw (Word variations have been searched)
#25body near/3 (cool* or cold*):ti,ab,kw (Word variations have been searched)
#26(#22 or #23 or #24 or #25)
#27(#21 and #26)
#28MeSH descriptor: [CranioCerebral Trauma] explode all trees
#29MeSH descriptor: [Cerebrovascular Trauma] explode all trees
#30MeSH descriptor: [Brain Edema] explode all trees
#31MeSH descriptor: [Glasgow Coma Scale] explode all trees
#32MeSH descriptor: [Glasgow Outcome Scale] explode all trees
#33MeSH descriptor: [Unconsciousness] explode all trees
#34glasgow near/3 scale*:ti,ab,kw (Word variations have been searched)
#35Unconscious* or coma* or concuss* or 'persistent vegetative state':ti,ab,kw (Word variations have been searched)
#36Rancho Los Amigos Scale:ti,ab,kw (Word variations have been searched)
#37(head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near/3 (injur* or trauma* or damag* or wound* or fracture* or contusion*):ti,ab,kw (Word variations have been searched)
#38Diffuse axonal injur*:ti,ab,kw (Word variations have been searched)
#39(#37 or #38)
```

#40(#32 or #33 or #34 or #35 or #36)

#41(#39 and #40)

#42(#28 or #29 or #30 or #39 or #41)

MEDLINE (OvidSP)

1. exp CRANIOCEREBRAL TRAUMA/

2. exp Cerebrovascular Trauma/

3. exp BRAIN EDEMA/

4. exp GLASGOW COMA SCALE/

5. exp GLASGOW OUTCOME SCALE/

6. exp UNCONSCIOUSNESS/

7. (glasgow adj3 scale*).ab,ti.

8. (Unconscious* or coma* or concuss* or 'persistent vegetative state').ab,ti.

9. Rancho Los Amigos Scale.ab,ti.

10. ((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.

11. Diffuse axonal injur\$.ab,ti.

12. 10 or 11

13. 4 or 5 or 6 or 7 or 8 or 9

14. 12 and 13

15. (therapy or surgery or rehabilitation or diet therapy or drug therapy or Prevention & Control).fs.

16. 12 and 15

17. 1 or 2 or 3 or 14 or 16

18. exp Hypothermia/

19. exp Hypothermia, Induced/

20. exp Cryotherapy/

21. (hypotherm\$ or cryotherap\$).ab,ti.

22. ((cool* or cold) adj3 (therap* or device* or equipment)).ab,ti.

23. (temperature adj3 reduc*).ab,ti.

24. (intravenous adj3 (cold or cool*) adj3 (fluid* or catheter*)).ab,ti.

25. ((cool* or cold*) adj3 (blanket* or neck collar* or helmet* or hood*)).ab,ti.

26. ice-water lavage.ab,ti.

27. or/18-26

28. exp Analgesics, Non-Narcotic/

29. (analgesic* adj3 (non?narcotic* or non?opioid*)).ab,ti.

30. exp Acetaminophen/

31. antipyretic\$.ab,ti.

32. (Aspirin or Meclofenamate sodium or Niflumic acid or Tiaprofenic acid or Tolfenamic acid or Acemetacine or Naproxen or Diclofenac or Etodolac or Fentiazac or Etofenamato or Fenbufen or Fentiazac or Nimesulid or Flurbiprofen or Ibuprofen or Indomethacin or Sulindac or ketoprofen or Lonazolac or Piroxicam or Tenoxicam or Proglumetacina or acetaminophen or paracetamol or acetamidophenol or hydroxyacetanilide or apap or acamol or acephen or acetaco or acetaminophen or algotrotyl or anacin-3 or datril or n-4-hydroxyphenyl acetanilide or n-acetyl-p-aminophenol or panadol or Tylenol or p-acetamidophenol).ab,ti.

33. exp Anti-Inflammatory Agents, Non-Steroidal/

34. ((analgesic* or non?steroidal) adj3 anti?inflammator*).ab,ti.

35. (NSAID* or anti?rheumatic* or aspirin-like).ab,ti.

36. or/28-35

37. exp Body Temperature/

38. exp Body Temperature Regulation/

39. (body adj3 temperature).ab,ti.

40. (body adj3 (cool* or cold*)).ab,ti.

41. or/37-40

42. 36 and 41

43. 27 or 42

44. 17 and 43

45. randomi?ed.ab,ti.

46. randomized controlled trial.pt.

47. controlled clinical trial.pt.

48. placebo.ab.

49. clinical trials as topic.sh.

50. randomly.ab.

51. trial.ti.

52. or/45-51
53. (animals not (humans and animals)).sh.
54. 52 not 53
55. 44 and 54

Embase (OvidSP)

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').ab,ti.
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 INDUCED HYPOTHERMIA/
16. exp HYPOTHERMIA/
17. exp cryotherapy/
18. (hypotherm\$ or cryotherap\$).ab,ti.
19. ((cool\$ or cold) adj3 (therap\$ or device\$ or equipment)).ab,ti.
20. (temperature adj3 reduc\$).ab,ti.
21. (intravenous adj3 (cold or cool\$) adj3 (fluid\$ or catheter\$)).ab,ti.
22. ((cool\$ or cold\$) adj3 (blanket\$ or neck collar\$ or helmet\$ or hood\$)).ab,ti.
23. ice-water lavage.ab,ti.
24. or/15-23
25. (analgesic\$ adj3 (non?narcotic\$ or non?opioid\$)).ab,ti.
26. exp Paracetamol/
27. antipyretic\$.ab,ti.
28. (Aspirin or Meclofenamate sodium or Niflumic acid or Tiaprofenic acid or Tolfenamic acid or Acemetacine or Naproxen or Diclofenac or Etodolac or Fentiazac or Etofenamato or Fenbufen or Fentiazac or Nimesulid or Flurbiprofen or Ibuprofen or Indomethacin or Sulindac or ketoprofen or Lonazolac or Piroxicam or Tenoxicam or Proglumetacina or acetaminophen or paracetamol or acetamidophenol or hydroxyacetanilide or apap or acamol or acephen or acetaco or acetaminophen or algotropyll or anacin-3 or datril or n-4-hydroxyphenyl acetanilide or n-acetyl-p-aminophenol or panadol or Tylenol or p-acetamidophenol).ab,ti.
29. exp Nonsteroid Antiinflammatory Agent/
30. exp Antipyretic Analgesic Agent/
31. ((analgesic\$ or non?steroidal) adj3 anti?inflammator\$).ab,ti.
32. (NSAID\$ or anti?rheumatic\$ or aspirin-like).ab,ti.
33. or/25-32
34. exp body temperature/
35. exp Thermoregulation/
36. (body adj3 temperature).ab,ti.
37. (body adj3 (cool\$ or cold\$)).ab,ti.
38. or/34-37
39. 33 and 38
40. 24 or 39
41. 14 and 40
42. exp Randomized Controlled Trial/
43. exp controlled clinical trial/
44. randomi?ed.ab,ti.
45. placebo.ab.
46. Clinical Trial/
47. randomly.ab.
48. trial.ti.
49. or/42-48

50. exp animal/ not (exp human/ and exp animal/)

51. 49 not 50

52. 41 and 51

ISI Web of Science (SCI-EXPANDED; CPCI-S)

#35 #34 AND #29

#34 #33 AND #32

#33 TS=((human*))

#32 #31 OR #30

#31 TS=((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 TS=((controlled clinical trial OR controlled trial OR clinical trial OR placebo))

#30 TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))

#29 #28 AND (#19 or #9)

#28 #27 OR #25

#27 #26 AND #25

#26 #22 OR #21 OR #20

#25 #24 OR #23

#24 TS=("Diffuse axonal injur*")

#23 TS=((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) near/3 (injur* or trauma* or damag* or wound* or fracture* or contusion*))

#22 TS=(Rancho Los Amigos Scale)

#21 TS=(Unconscious* or coma* or concuss* or 'persistent vegetative state')

#20 TS=(glasgow near/3 scale*)

#19 #18 AND #15

#18 #17 OR #16

#17 TS=(body near/3 (cool* or cold*))

#16 TS=(body near/3 temperature)

#15 #14 OR #13 OR #12 OR #11 OR #10

#14 TS=(NSAID* or anti-rheumatic* or aspirin-like)

#13 TS=((analgesic* or non-steroidal) near/3 (anti-inflammatory*))

#12 TS=(Aspirin or Meclofenamate sodium or Niflumic acid or Tiaprofenic acid or Tolfenamic acid or Acemetacine or Naproxen or Diclofenac or

Etodolac or Fentiazac or Etofenamato or Fenbufen or Fentiazac or Nimesulid or Flurbiprofen or Ibuprofen or Indomethacin or Sulindac or ketoprofen

or Lonazolac or Piroxicam or Tenoxicam or Proglumetacina or acetaminophen or paracetamol or acetamidophenol or hydroxyacetanilide or apap or

acamol or acephen or acetaco or acetaminophen or algotropyl or anacin-3 or datril or n-4-hydroxyphenyl acetanilide or n-acetyl-p-aminophenol or

panadol or Tylenol or p-acetamidophenol)

#11 TS=(antipyretic*)

#10 TS=(analgesic* near/3 (non-narcotic* or non-opioid*))

#9 #8 OR #7 OR #6 OR #3 OR #2 OR #1

#8 TS=(ice-water lavage)

#7 TS=((cool* or cold*) near/3 (blanket* or "neck collar*" or helmet* or hood*))

#6 #5 AND #4

#5 TS=(fluid* or catheter*)

#4 TS=(intravenous near/3 (cold or cool*))

#3 TS=((temperature near/3 reduc*))

#2 TS=((cool* or cold) near/3 (therap* or device* or equipment))

#1 TS=(hypotherm* or cryotherap*)

PubMed

((((((((((intravenous[title/abstract] AND (cold[title/abstract] OR cool*[title/abstract]) AND (fluid*[title/abstract] OR catheter*[title/abstract])) OR ice-water lavage[Title/Abstract]) OR ((temperature[Title/Abstract]) AND reduc*[Title/Abstract])) OR ((hypotherm*[Title/Abstract]) OR cryotherap*[Title/Abstract])) OR (((((((blanket*[Title/Abstract]) OR helmet*[Title/Abstract]) OR hood*[Title/Abstract]) OR fluid*[Title/Abstract]) OR catheter*[Title/Abstract]) OR neck collar*[Title/Abstract])) AND ((cool*[Title/Abstract]) OR cold*[Title/Abstract])) AND (((((((("Comparative Study"[Publication Type]) OR "Randomized Controlled Trial"[Publication Type]) OR "Controlled Clinical Trial"[Publication Type])) OR (((((((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]) OR group[Title/Abstract])) NOT ("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh])))) AND (((((((((((head[Title/Abstract]) OR crani*[Title/Abstract]) OR cerebr*[Title/Abstract])

OR capitis[Title/Abstract] OR brain*[Title/Abstract] OR forebrain*[Title/Abstract] OR skull*[Title/Abstract] OR hemispher*[Title/Abstract] OR intracran*[Title/Abstract] OR intercran*[Title/Abstract] OR (((haematoma*[Title/Abstract] OR hematoma*[Title/Abstract] OR haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract] OR bleed*[Title/Abstract] OR pressur*[Title/Abstract])) AND (head[Title/Abstract] OR crani*[Title/Abstract] OR cerebr*[Title/Abstract] OR brain*[Title/Abstract] OR intra?cran*[Title/Abstract] OR inter?cran*[Title/Abstract] OR intracran*[Title/Abstract] OR intercran*[Title/Abstract])) OR (((glasgow outcome scale[Title/Abstract] OR glasgow coma scale[Title/Abstract] OR rancho los amigos scale[Title/Abstract] OR ((diffuse axonal injury[Title/Abstract] OR diffuse axonal injuries[Title/Abstract] OR ((brain[Title/Abstract] OR cerebral[Title/Abstract] OR intracranial[Title/Abstract]) AND (oedema[Title/Abstract] OR edema[Title/Abstract] OR swell*[Title/Abstract])) OR ((unconscious*[Title/Abstract] OR coma*[Title/Abstract] OR concuss*[Title/Abstract]) AND (injur*[Title/Abstract] OR trauma*[Title/Abstract] OR damag*[Title/Abstract] OR wound*[Title/Abstract] OR fracture*[Title/Abstract] OR contusion*[Title/Abstract] OR haematoma*[Title/Abstract] OR hematoma*[Title/Abstract] OR haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract] OR pressur*[Title/Abstract])) OR (((Coma[Mesh])) AND (injur*[title/abstract] OR trauma*[title/abstract] OR damag*[title/abstract] OR wound*[title/abstract] OR fractur*[title/abstract] OR contusion*[title/abstract] OR haematoma*[title/abstract] OR hematoma*[title/abstract] OR haemorrhag*[title/abstract] OR hemorrhag*[title/abstract] OR pressur*[title/abstract] OR lesion*[title/abstract] OR destruction*[title/abstract] OR oedema*[title/abstract] OR edema*[title/abstract] OR contusion*[title/abstract] OR concus*[title/abstract])))) AND publisher[sb]

WHAT'S NEW

Date	Event	Description
23 February 2020	New citation required and conclusions have changed	<p>Two new authors (Philip Baker and Sharon Lewis) contributed to the review.</p> <p>We updated the searches, identified one eligible study and incorporated this study into the review. We also identified four ongoing studies. One study is awaiting classification as it was published as an abstract with insufficient information to enable inclusion in the review and we were unable to make contact with the study authors.</p> <p>We updated the text in the review to account for changes in Cochrane methodological reporting standards and to improve clarity.</p> <p>We changed the title (formerly 'Modest cooling therapies (35 °C to 37.5 °C) for traumatic brain injury').</p>

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 3, 2008

Date	Event	Description
20 October 2014	Amended	Minor edits made to the text to improve clarity.
21 August 2014	Amended	All declaration of interest statements from the authors are now included in the review.
31 July 2014	New citation required but conclusions have not changed	The authors of the review have changed.
31 July 2014	New search has been performed	<p>The search for studies has been updated to 23 September 2013.</p> <p>One ongoing study was identified (NCT01231139a), and its results will be included into the review by the end of 2015.</p>

Date	Event	Description
5 September 2007	New citation required and major changes	Protocol first published.

CONTRIBUTIONS OF AUTHORS

PB: assessed the trials for inclusion and extracted data; drafted and revised the review.

SL: assessed the trials for inclusion and extracted data; drafted and revised the review.

MS: conceived and designed the review; drafted and revised the previous version of the review according to comments; contacted pharmaceutical companies during the previous versions; approved the final version.

NH: assessed the trials for inclusion criteria (previous version; [Saxena 2014](#)); approved the final version.

KD: assessed the trials for inclusion criteria (previous version; [Saxena 2014](#)); approved the final version.

AC: assessed the trials for inclusion (previous version; [Saxena 2007](#)); approved the final version.

PA: conceived the review; assessed the trials for inclusion (previous version; [Saxena 2014](#)); approved the final version.

DECLARATIONS OF INTEREST

SL: none known.

PB: none known.

PA: I am chief investigator of an international clinical trial of titrated therapeutic hypothermia to reduce intracranial pressure after traumatic brain injury (NIHR HTA Funded).

AC: none known.

KD: I am an Intensive Care Doctor involved in the treatment of people with head injury. I am also involved in other academic research in the area of head injury.

NH: none known.

MS: I am engaged in an investigator-initiated research program to answer the question of whether normothermia reduces death and disability after acute neurological illnesses (PARITY Study).

SOURCES OF SUPPORT

Internal sources

- Professor Peter Andrews, UK

Supported by the University of Edinburgh

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The title has been changed (formerly 'Modest cooling therapies (35 °C to 37.5 °C) for traumatic brain injury').
- Authors: two new authors were added to the review (PB and SL).
- Background: we updated this section to incorporate more recent references, and used standard Cochrane subheadings. We updated the text to fit these subheadings.
- Objectives: we reworded the objectives, to improve use of consistent terms throughout the review. Some information in this section was better positioned in the methods section, so we removed some text.
- Types of studies: for clarification, we specified the inclusion of quasi-randomised trials. We clarified the inclusion of abstracts in the event that sufficient information was available.

- Types of participants: for clarification, we specified the inclusion of participants of any age. We specified that we would include mixed populations if data were available only for participants with TBI.
- Types of interventions: for clarification, we specified the exclusion of studies that had the intention of cooling within ranges that crossed the threshold of 35 °C (for sample cooling range between 36 °C and 34 °C). We specified that physical therapies and drug therapies would be managed and reported as separate comparison groups.
- Outcomes: we clarified the range of GOS scores (one to three on the 5-point scale) that indicate a poor outcome. We moved a paragraph relating to information size of the primary outcome to the section related to precision of the estimate ('[Summary of findings 1](#) and GRADE).
- Search methods: in this update, we did not search the Cochrane Injuries Group Specialised Register, the National Research Register, or Zetoc (strategies searched in previous versions of the review are included in [Appendix 1](#)). We did not contact organisations previously contacted (see [Appendix 2](#)).
- Subgroup analysis: we did not conduct subgroup analysis because we found fewer than 10 studies. In the methods section, we clarified that our decision to conduct subgroup analysis would be based on the number of studies.
- Sensitivity analyses: we explained that sensitivity analyses had not been planned, nor was it feasible for us to conduct any because we had insufficient studies. We reported planned sensitivity analyses for future updates, to evaluate the potential effects of selection bias and meta-analytic effects model.
- Measures of treatment effect: the outcomes in this review are currently only intended to be collected using dichotomous data, and we therefore removed text relating to continuous outcome data as it was not relevant to the current review outcomes.

NOTES

In future updates of this review, we will assess some outcomes at the end of the follow-up period as reported in the studies. However, if these differ substantially between the included studies, we will group studies into similar, clinically meaningful follow-up periods, and will report results separately for short-, medium-, and long-term outcomes as necessary.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*administration & dosage]; Antipyretics [*administration & dosage]; Bias; *Body Temperature [drug effects]; Brain Injuries, Traumatic [mortality] [*therapy]; Hypothermia, Induced [*methods] [mortality]; Injections, Intravenous; Placebos

MeSH check words

Adult; Humans