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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	6
OBJECTIVES	7
METHODS	7
Figure 1.	8
Figure 2.	9
Figure 3.	10
RESULTS	10
DISCUSSION	12
AUTHORS' CONCLUSIONS	13
ACKNOWLEDGEMENTS	13
REFERENCES	14
CHARACTERISTICS OF STUDIES	17
DATA AND ANALYSES	21
Analysis 1.1. Comparison 1 Intraoperative mild hypothermia compared with control (no hypothermia), Outcome 1 Death or dependency in activities of daily living 3 months post-operatively in all participants.	22
Analysis 1.2. Comparison 1 Intraoperative mild hypothermia compared with control (no hypothermia), Outcome 2 Absolute effect on death or dependency in activities of daily living 3 months post-operatively in all participants.	22
APPENDICES	22
WHAT'S NEW	23
CONTRIBUTIONS OF AUTHORS	23
DECLARATIONS OF INTEREST	23
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	23
INDEX TERMS	24

[Intervention Review]

Intraoperative mild hypothermia for postoperative neurological deficits in people with intracranial aneurysm

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ABSTRACT

Background

Rupture of an intracranial aneurysm causes aneurysmal subarachnoid haemorrhage, which is one of the most devastating clinical conditions. It can be classified into five Grades using the Hunt-Hess or World Federation of Neurological Surgeons (WFNS) scale. Grades 4 and 5 predict poor prognosis and are known as 'poor grade', while grade 1, 2, and 3 are known as 'good grade'. Disturbances of intracranial homeostasis and brain metabolism are known to play certain roles in the sequelae. Hypothermia has a long history of being used to reduce metabolic rate, thereby protecting organs where metabolism is disturbed, and may potentially cause harm.

Objectives

To assess the effect of intraoperative mild hypothermia on postoperative death and neurological deficits in people with ruptured or unruptured intracranial aneurysms.

Search methods

We updated the search in the Cochrane Stroke Group Trials Register (August 2015), the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 8), WHO International Clinical Trials Registry Platform (ICTRP; December 2015), MEDLINE (1950 to September 2015), EMBASE (1980 to September 2015), Science Citation Index (1900 to September 2015), and 11 Chinese databases (September 2015). We also searched ongoing trials registers (September 2015) and scanned reference lists of retrieved records.

Selection criteria

We included only randomised controlled trials that compared intraoperative mild hypothermia (32°C to 35°C) with control (no hypothermia) in people with ruptured or unruptured intracranial aneurysms.

Data collection and analysis

Two review authors independently selected trials and assessed the risk of bias for each included study. We presented data as risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CI).

Main results

We included three studies, enrolling 1158 participants. Each study reported an increased rate of recovery with intraoperative mild hypothermia, but the effect sizes were not sufficient for certainty. A total of 1086 of the 1158 participants (93.8%) had good grade aneurysmal subarachnoid haemorrhage. Seventy-six of 577 participants (13.1%) who received hypothermia and 93 of 581 participants

(16.0%) who did not receive hypothermia were dead or dependent (RR 0.82; 95% CI 0.62 to 1.09; RD -0.03; 95% CI -0.07 to 0.01, moderate-quality evidence) after three months.

Reported unfavourable outcomes did not differ between participants with or without hypothermia. The quality of evidence for these outcomes remains unclear because the outcomes were reported in a variety of ways. No decompressive craniectomy or corticectomy was reported. Thirty-six of 577 (6.2%) participants with hypothermia and 40 of 581 (6.9%) participants without hypothermia had infarction. Thirty-four of 577 (6%) participants with hypothermia and 32 of the 581 (5.5%) participants without hypothermia had clinical vasospasm (temporary deficits).

Duration of hospital stay was not reported. Only one study with 112 participants reported discharge destinations: 43 of 55 (78.2%) participants with hypothermia and 39 of 57 (68.4%) participants in the control group were discharged home. The remaining participants were discharged to other facilities.

Thirty-nine of 577 (6.8%) participants with hypothermia and 39 of 581 (6.7%) participants without hypothermia had infections. Six of 577 (1%) participants with hypothermia and 6 of 581 (1%) participants without hypothermia had cardiac arrhythmia.

Authors' conclusions

It remains possible that intraoperative mild hypothermia could prevent death or dependency in activities of daily living in people with good grade aneurysmal subarachnoid haemorrhage. However, the confidence intervals around this estimate include the possibility of both benefit and harm. There was insufficient information to draw any conclusions about the effects of intraoperative mild hypothermia in people with poor grade aneurysmal subarachnoid haemorrhage or without subarachnoid haemorrhage. We did not identify any reliable evidence to support the routine use of intraoperative mild hypothermia. A high-quality randomised clinical trial of intraoperative mild hypothermia for postoperative neurological deficits in people with poor grade aneurysmal subarachnoid haemorrhage might be feasible.

PLAIN LANGUAGE SUMMARY

Cooling the brain during surgery to prevent death or severe disability in people with brain aneurysms

Review question

We reviewed the evidence about the effect of cooling the brain during surgery for brain aneurysms. We found three studies of acceptable quality and analysed the results to see if cooling the brain during open-skull surgery for brain aneurysms prevents death or severe disability.

Background

Intracranial aneurysms are bulges on the cerebral arterial wall. Rupture of an intracranial aneurysm is often life-threatening. People with intracranial aneurysms are classified as good grade or poor grade, based on their clinical manifestations. Surgery is a common option to treat this problem, but it can cause further damage to the brain. Theoretically, cooling the brain reduces its metabolic activity, thus protecting it during an operation. Research on animals supports this theory in general.

Study characteristics

The updated evidence is current to August 2015. We found only three appropriate studies with a total of 1158 participants to include. Data primarily came from one high-quality study with 1000 participants.

Key results

Our analysis showed that in good grade patients, it remains possible that cooling the brain during surgery might prevent death or dependency in everyday activities. Very limited information was available for those without bleeding or those with poor grade bleeding. Unfavourable outcomes did not differ between participants with or without hypothermia. The quality of evidence for these outcomes remains unclear because they were reported in a variety of ways.

Quality of the evidence

We do not have enough data to be certain about the effect of cooling on death or dependency. The evidence for other outcomes was more uncertain, since we could not combine the data due to variation in the definition and reporting of outcome data. Data in our analyses were primarily from one high quality trial on good grade participants.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Intraoperative mild hypothermia compared with control for postoperative neurological deficits

Patient or population: people with intracranial aneurysm

Settings: in-hospital

Intervention: intraoperative mild hypothermia

Comparison: no intraoperative mild hypothermia

Outcomes	Absolute effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Death or dependency in ADL 3 months post-operatively	RD-0.03 (-0.07 to 0.01)	1164 (3)	+++ Moderate	Most information is from Todd 2005 , which is judged to be at low risk of bias. Relative effect RR 0.82, 95% CI 0.62 to 1.09
Decompressive craniectomy or corticectomy performed to reduce intracranial pressure during the surgery				Decompressive craniectomy or corticectomy performed to reduce intracranial pressure were not reported
Newly developed postsurgical vasospasm or infarction during hospitalisation		1164 (3)		<p>Chouhan 2006</p> <ul style="list-style-type: none"> hypothermic participants: 3 clinical vasospasms, 1 infarct normothermic group: 4 vasospasms 2 infarcts <p>Hindman 1999</p> <ul style="list-style-type: none"> hypothermia group: 4/24 with SAH have persistent deficits; 8/24 with SAH have temporary deficits; 1/31 without SAH have persistent deficits; 0/31 without SAH have temporary deficits normothermic group: 10/27 with SAH have permanent deficits; 6/27 with SAH have temporary deficits; 2/29 without SAH have permanent deficits; 0/29 without SAH have temporary deficits <p>Todd 2005</p> <ul style="list-style-type: none"> 23 participants in the hypothermia group and 22 participants in the normothermia group had delayed ischaemic neurological deficits 26 in the hypothermia group and 30 in the control group had delayed infarction

		<ul style="list-style-type: none"> due to wide heterogeneity in this outcome among studies, we did not pool the data
Duration of hospitalisation	114 (1)	<p>Hindman 1999: data were not available for calculating the 95% CI of mean hospitalisation days</p> <p>Participants with SAH</p> <ul style="list-style-type: none"> intervention group: 17 days comparison group: 16 days <p>Participants without SAH</p> <ul style="list-style-type: none"> intervention group: 4 days comparison group: 5 days
Destination of discharge (home or to another hospital)	114 (1)	<p>Hindman 1999</p> <ul style="list-style-type: none"> hypothermia group: 18/24 with SAH discharged to home; 5/24 with SAH discharged to other facilities; 25/31 without SAH discharged home; 4/31 without SAH discharged to other facilities normothermic group: 16/28 with SAH discharged home; 10/28 with SAH discharged to other facilities; 23/29 without SAH discharged home; 6/29 without SAH discharged to other facilities
Postoperative infection of the wound, the lung, the urinary tract, or the skin within one week after surgery	1164 (3)	<p>Chouhan 2006</p> <ul style="list-style-type: none"> hyperthermia group: 3 participants had meningitis normothermia group: 2 participants in had meningitis <p>Hindman 1999</p> <ul style="list-style-type: none"> hypothermia group: 1/24 with SAH had pneumonia normothermic group: 3/27 with SAH had pneumonia none of the participants without SAH had pneumonia <p>Todd 2005</p> <ul style="list-style-type: none"> 2 participants in each group had Incision or bone-flap infections 6 participants in the hypothermia group and 4 participants in the control group had meningitis or ventriculitis 5 participants in the hypothermia group and 3 participants in the control group had bacteraemia 7 participants in each group had pneumonia 15 participants in the hypothermia group and 18 participants in the control group had urinary tract infection
Cardiac arrhythmia or arrest within	1047 (2)	<p>Chouhan 2006</p> <p>hypothermia group: 1 had premature ventricular contraction (33.2°C)</p>

one week after
surgery

Todd 2005

5 participants in the hypothermia and 6 in the control group had cardiac arrhythmia

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Data in our analysis were primarily from one high-quality study on people with good-grade aneurysmal subarachnoid haemorrhage. Thus, it is imprecise for death or dependency in activities of daily living in all patients. The evidence quality for this outcome is downgraded to moderate.

ADL: activities of daily living

CI: confidence interval

RR: risk ratio

SAH: subarachnoid haemorrhage

BACKGROUND

Description of the condition

An intracranial aneurysm forms at a weakened spot on the wall of a main intracranial artery and enlarges with circulating blood pressure, similar to the inflation of a balloon. It is usually located on the basilar surface of the brain. However, it is not known if or when it will rupture. The rupture of intracranial aneurysms is not only disastrous for patients, but is also a devastating situation for clinicians. Sudden internal bleeding within the skull, as well as the resulting complications, has caused death in 8.3% to 66.7% of those participants reported in various studies. A marked variance in case-fatality rates has been recognised among studies conducted on different populations: for example, the case fatality in Japan is 8.3%, 11.5% lower than the case fatality rate of Europe, the USA, Australia, and New Zealand at 19.8% (Hop 1997; Nieuwkamp 2009; Vega 2002).

Fortunately, not all intracranial aneurysms are life-threatening. In fact, an intracranial aneurysm is not a rare condition. Although reports on the prevalence of unruptured intracranial aneurysms vary widely from 2 to 90 per 1000 people (Griffiths 1996; McCormick 1965), a prospective angiography study has estimated it at 6% in the general population (Rinkel 1998). The risk of rupture for an intracranial aneurysm has been linked to a series of factors including: old age, female gender, the ethnicity of the person, whether the size of the aneurysm is larger than one centimetre in diameter, posterior circulatory location, and probably the non-spherical configuration of the circle of Willis and direct blood flow into the cavity of the aneurysm (Rinkel 1998; Rooij 2009; Wermer 2007; Wiebers 2003). Among those factors, the size of the unruptured aneurysm is of particular significance. For example, one international study indicated that the cumulative risk of rupture for aneurysms that were less than 10 mm in diameter at diagnosis was less than 0.05% per year, while 6% of those with a diameter more than 25 mm were likely to burst in the first year of diagnosis (Investigators 1998).

As a matter of course, the rupture of an intracranial aneurysm will be followed by the leakage of blood into the extravascular space, which most commonly takes the form of a diffused subarachnoid haemorrhage (Suarez 2006), occasionally accompanied by an intraventricular haemorrhage (Rosen 2007), or more rarely, an intra-parenchymal haematoma (Abbed 2003). The blood clot causes severe damage to the brain. However, a much more hazardous consequence of the rupture of a cerebral aneurysm is the deleterious cascades of damage upon the vascular system, following the disturbance of the auto-regulation of the intracranial blood circulation. Vascular malfunction, in turn, causes ischaemic damage to the neurons. The pathophysiological response by the circulatory system to the rupture is a profound reduction and fluctuation of blood flow to the brain tissue, which causes a hypoxic insult to it through an alteration of the levels of certain intermediate substances (Prunell 2004; Sehba 2006). The brain is extremely vulnerable to oxygen deficiency, thus, deprivation of oxygen will lead to necrosis and apoptosis of affected neurons, giving rise to life-threatening brain oedema and leaving the patient with neurological deficits (Claassen 2002). There are different scales to assess the clinical severity of subarachnoid haemorrhage, based on manifestations of patients, such as Hunt-Hess grade (Hunt 1968), and the World Federation of Neurological Sciences (WFNS) grade (Teasdale 1988). Both scales divide people with aneurysmal

subarachnoid haemorrhage into five grades, with Grades 4 and 5 classified as 'poor grades' because they predict dismal prognoses. The other three grades are known as 'good grades'.

Unruptured intracranial aneurysms are usually asymptomatic, unless they are big enough to compress the nearby nerves or brain tissues. The resulting manifestations from mass effect include headache, seizure, visual loss, and facial pain (Raps 1993). It has been reported that severe headache occurring in an unusual location could be a warning symptom of impending aneurysmal subarachnoid haemorrhage (Ostergaard 1991). The benefit of screening for, or treatment of, unruptured intracranial aneurysms is controversial and must be weighed cautiously against a surgery-related morbidity and mortality rate of about 15%, especially for older people (Gerlach 2007; Investigators 1998; Study Group 1999). One recent cost-effective analysis from the Netherlands concluded that patients' life expectancy, risk of rupture, and utility of awareness of an untreated aneurysm are the outcomes that mainly define cost-effectiveness for treating unruptured aneurysms in that region (Greving 2009).

Treatment to prevent re-bleeding of a ruptured aneurysm, or the rupture of a vulnerable unruptured intracranial aneurysm, is either surgical clipping with craniotomy or endovascular coiling. The choice of treatment is based on the general condition of the patient and the location of the aneurysm, as well as the specific circumstances in different hospitals (Johnston 2002; Takao 2008; Vega 2002). For surgical treatment of ruptured intracranial aneurysms, one of the priorities for surgeons is to prevent and manage the ischaemic events that result from cerebral vasospasm, or occasionally, from the temporary deliberate occlusion of the feeding artery to facilitate the clipping process (Haley Jr 1992; Kassell 1984). As we have mentioned, the ensuing oedema of the brain after anoxic damage is a devastating emergency, which sometimes warrants a decompressive cricectomy or a craniectomy to prevent lethal brain herniation (Jha 2003). Inevitably, both infarction and decompressive removal of the brain tissue will be followed by certain neurological deficits.

Description of the intervention

Profound intraoperative hypothermia, with a temperature lower than 28°C, was attempted in the 1950s to protect brain function from surgery-related ischaemic damage. However, this method has not been generally accepted due to its fatal complications (Chouhan 2006; Todd 2005). In the 1980s, the interest in hypothermia was re-ignited when the application of mild hypothermia in place of deep hypothermia was introduced. In clinical practice, the target temperature varies from 32°C to 35°C; the method and timing of cooling and re-warming are also quite variable.

Numerous animal experiments have demonstrated a beneficial effect on brain protection from ischaemic damage by mild hypothermia (Busto 1987; Busto 1989; Clifton 1991; Dempsey 1987; Dietrich 1990; Minamisawa 1990; Patel 1994; Shimohata 2007; Zhang 1993; Zhao 2007). However, it has been reported that hypothermia can predispose the patient to wound infection and lead to a longer stay in hospital (Kurz 1996). Animal experiments have also shown a decreased resistance to bacterial infection of the skin under deliberate hypothermia (Sheffield 1994a; Sheffield 1994b). More serious than potential infections, hypothermia probably disturbs the electrical equilibrium of the myocardium

and causes dangerous cardiac arrhythmia, or even cardiac arrest (Freysz 1989).

How the intervention might work

Experiments on animals have proven that mild hypothermia suppresses the complex harmful biochemical cascades related to inflammation and alters blood-brain barrier permeability after experimental stroke and brain damage (Deng 2003). The activity of a great number of identified biochemical agents associated with ischaemic damage has been shown to be influenced by mild hypothermia in favour of neuronal protection (Busto 1989; Dempsey 1987; Dietrich 1990; Patel 1994; Shimohata 2007; Zhao 2007). A diminished degree of brain oedema following ischaemia due to mild hypothermia has also been specifically demonstrated in rats (Dempsey 1987; Kawanishi 2008; Schubert 2008; Török 2009). Studies on human patients have already shown that mild intraoperative hypothermia reduces the production of reactive oxygen intermediates by polymorphonuclear leukocytes, thereby attenuating the damage to cells during the process of inflammation (Wenisch 1996).

Why it is important to do this review

Although numerous studies on the effect of hypothermia for brain-protection have been done during the past decades, we still lack a consensus on whether intraoperative hypothermia is effective in reducing neurological deficits relating to the surgical treatment of intracranial aneurysms. A systematic review will inform decision making or suggest that further studies are required.

OBJECTIVES

To assess the effect of intraoperative mild hypothermia on postoperative neurological deficits in people with ruptured and unruptured intracranial aneurysm.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing mild hypothermia with no hypothermia.

Types of participants

People with ruptured or unruptured intracranial arterial aneurysm undergoing craniotomy.

Types of interventions

Intraoperative mild hypothermia (32°C to 35°C) compared with control (no hypothermia). We did not specify the methods or restrict any co-intervention in inducing and maintaining hypothermia.

Types of outcome measures

Primary outcomes

The primary outcome was death or dependency in activities of daily living (ADL) three months post-operatively, recorded at the end of scheduled follow-up, quantified through standard scales, for example the Rankin scale (Wilson 2005), the Barthel Index (Sulter

1999), or the Glasgow Outcome Scale (GOS; Jennett 1975). The GOS divides recovery into five levels:

1. dead;
2. vegetative state;
3. severe disability (able to follow commands but unable to live independently);
4. moderate disability (able to live independently but unable to return to work or school);
5. good recovery (able to return to work or school).

Secondary outcomes

1. Decompressive craniectomy or corticectomy performed to reduce intracranial pressure during the surgery.
2. Newly developed postsurgical vasospasm or infarction during hospitalisation.
3. Duration of hospitalisation.
4. Destination of discharge (home or to another hospital).
5. Postoperative infection of the wound, the lung, the urinary tract, or the skin within one week after surgery.
6. Cardiac arrhythmia or arrest within one week after surgery.

Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module. We did not restrict the searches by date, publication status, or language, and arranged translation of studies where necessary.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched for this update by the Managing Editor in August 2015. We also searched the following electronic bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 8);
- MEDLINE (1950 to September 2015; [Appendix 1](#));
- EMBASE (1980 to September 2015);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index-Science (CPCI-S) (1900 to September 2015);
- The WHO International Clinical Trials Registry Platform (ICTRP; <http://www.who.int/ictip/en/>);
- Chinese Bio-Medical Literature & Retrieval System (CBM; 1979 to September 2015)
- China National Knowledge Infrastructure (CNKI; searched September 2015);
- Chinese Dissertations database (CDDb; searched September 2015);
- Chinese MD and DD Dissertations in CNKI (searched September 2015);
- Chinese Science and Technology Document Databases (CSTDB; searched September 2015);
- Chinese scientific periodical database of VIP Information (searched September 2015);
- Chinese Social Science Citation Index (searched September 2015);

- Wanfang Data (<http://www.wanfangdata.com/>; searched September 2015).

The MEDLINE search strategy was developed by the Cochrane Stroke Group Trials Search Co-ordinator.

We used the following search terms for EMBASE and Science Citation Index: "hypothermia" and "intracranial AND 'aneurysm'/exp" and used the same words translated into Chinese for the Chinese databases.

Searching other resources

In an effort to identify further published, unpublished and ongoing trials not available in the major databases, we:

- checked reference lists of all relevant articles;
- searched the following ongoing trials and research registers (searched September 2015):
 - Stroke Trials Registry (<http://www.strokecenter.org/trials/>);
 - ClinicalTrials.gov (<http://clinicaltrials.gov/>);

- Current Controlled Trials (<http://www.controlled-trials.com/>);

- searched the Internet using Baidu.com.

We had planned to search the Chinese Stroke Trials Register, but this was not available to us.

Data collection and analysis

Selection of studies

Two review authors (LR and BC) independently screened the titles and abstracts of the records obtained from the searches of the electronic databases and excluded obviously irrelevant studies. We obtained the full manuscripts of the remaining records for further checking and the same two review authors independently examined the designs of these studies, and then included those matching the inclusion criteria for reviewing. The two review authors resolved any disagreements through discussion with the third review author (CY). See [Figure 1](#) for the flow of studies identified.

Figure 1. Study flow diagram for 2015 update.

Data extraction and management

Two review authors (LR and BC) independently extracted data relevant to the objective of this review from the reports of included studies. The outcome data of interest included case fatality and the rate of severe disability (dependency in activities of daily living measured by the standard scales mentioned above), as well as the number of participants in the treatment and control groups. We also extracted information on the secondary outcomes listed above if they were reported.

Assessment of risk of bias in included studies

We assessed and reported sources of bias using Cochrane's tool for assessing risk of bias. We addressed the following domains ([Higgins 2011](#)):

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting.

We scored each domain as 'low risk', 'high risk' or 'unclear risk' of bias and reported them in a 'Risk of bias' table. We summarised and presented the judgments made in those domains ([Figure 2](#); [Figure 3](#)).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chouhan 2006	?	?	+	-	+	+
Hindman 1999	?	+	+	?	+	+
Todd 2005	+	+	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Measures of treatment effect

We calculated risk ratio (RR) and 95% confidence interval (CI) of death or dependency in ADL for each study.

Unit of analysis issues

We had planned to address unit of analysis issues when the number of observations in the analysis did not match the number of units that were randomised. However, none of the three included studies had unit of analysis issues.

Dealing with missing data

We recorded losses to follow-up. We regarded exclusions in the middle of a study as missing data. We sought reasons for missing data and made judgements on the influence of missing data according to information obtained from the study reports. We judged missing data to be random if they were deemed to be unrelated to outcome.

Assessment of heterogeneity

We assessed clinical and methodological diversity based on the study authors' judgement. When the confidence intervals for the results of individual studies have poor overlap, this generally indicates the presence of statistical heterogeneity; we looked at the baseline parameters of participants from each study, the methods used to achieve mild hypothermia, and data on the body temperature of participants during surgery. We also tested for statistical heterogeneity using the I^2 statistic.

Assessment of reporting biases

If there had been enough relevant studies, we had planned to produce funnel plots to investigate reporting bias. However, as we only included three studies, we were unable to do so.

Data synthesis

We generated a summarised RR and 95% CI for death or dependency in ADL using a random-effects meta-analysis provided by Review Manager 5.3 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We did not perform subgroup analyses for this update.

Sensitivity analysis

We recalculated the estimated risk ratio for Todd 2005 and compared it with the summarised estimation. We tested both the random-effects and fixed-effect models for the statistical estimation of risk difference.

RESULTS

Description of studies

Results of the search

Our searches of the electronic databases in English and Chinese identified 19 trials from the Cochrane Stroke Group Trials Register, and 1701 records from the other databases (165 from CENTRAL, 741 from MEDLINE, 610 from EMBASE, 176 from Science Citation Index, and 9 from Chinese databases; Figure 1). We found one relevant report in the Chinese databases and one ongoing study from the searches of the trials registers.

Included studies

Of the 11 seemingly relevant studies, only three met the inclusion criteria.

One study conducted in India included people with both good grade and poor grade subarachnoid haemorrhage (Chouhan 2006). The other two studies were, in fact, two stages of one trial performed by the same team of researchers in the USA (Hindman 1999; Todd 2005). They were both multicentre studies, with Hindman 1999 being the preliminary study and Todd 2005 the final study. All participants in Todd 2005 were newly enrolled. There was no duplication of data between these two studies.

The sample sizes of the three included studies varied from 70 to 1001 participants. They all reported that participants from both the hypothermia and normothermia groups had comparable

baseline characters of age, gender, weight, and other important factors. [Chouhan 2006](#) reported the results of 47 out of the 70 randomised participants; the exclusions were stated to be due to failures in achieving target temperature at the time of aneurysm clipping. [Hindman 1999](#) had intended to include 120 participants from four centres, with each contributing 30 participants, but one centre withdrew after having entered four participants; another substitute centre then contributed 20 participants instead. Of the 114 participants actually enrolled, 62 were operated on before the rupture of aneurysms, and three were lost to follow-up. [Todd 2005](#) enrolled 1001 participants, all with aneurysmal subarachnoid haemorrhage, and one was lost to follow-up. For more information, please refer to the [Characteristics of included studies](#) table.

Excluded studies

We excluded eight studies that initially appeared to be relevant because they turned out to be focusing on methods to achieve hypothermia and not to study the effects of hypothermia on neurological outcome. We excluded another study identified from the Chinese databases because none of the information needed to assess the quality of the study was reported and only one author was listed ([Zhang 2013](#)).

Risk of bias in included studies

[Chouhan 2006](#) had incomplete data, thus, the risk of bias was relatively high.

In [Hindman 1999](#), there were methodological flaws, which resulted in two unclear assessments for sequence generation and incomplete data; therefore, we assessed the overall risk of bias as high.

We evaluated the risk of bias of [Todd 2005](#) as low ([Figure 2](#); [Figure 3](#)).

Allocation

Only one of the three included studies specifically reported the method used for randomised sequence generation ([Todd 2005](#)) and allocation concealment. The randomised sequence was generated by a permuted-block scheme and the allocation was concealed in an opaque envelope, which was opened by the anaesthesiologist only after induction of anaesthesia.

Blinding

Surgeons in all three included studies were adequately blinded to the group assignments. Whether or not the participants and outcome assessors were adequately blinded was not reported.

Incomplete outcome data

In [Chouhan 2006](#), 23 participants were excluded because of failures in achieving the target temperature at the time of aneurysm clipping; three participants were lost to follow-up in [Hindman 1999](#); and one participant was lost to follow-up in [Todd 2005](#).

Selective reporting

All three included studies were free of selective reporting.

Other potential sources of bias

We did not suspect any other potential source of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#)

Primary outcomes

Death or dependency in activities of daily living in all patients

In total, 76 of 577 (13.2%) and 93 of 581 (16.0%) incidents of death or dependency occurred in the hypothermia and control groups, respectively. Since the studies contained both good-grade and poor-grade patients, we used a random-effects meta-analysis, which resulted in a summarised RR of 0.82 (95% CI 0.62 to 1.09; $P = 0.17$; [Analysis 1.1](#)). The RD was -0.03 (95% CI -0.07 to 0.01; $P = 0.17$; [Analysis 1.2](#)).

We did not detect significant statistical heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.11$, $\text{df} = 2$ ($P = 0.94$); $I^2 = 0\%$ ([Analysis 1.1](#)). We recalculated the estimated risk ratio for [Todd 2005](#) and compared it with the summarised estimation as a sensitivity analysis: the results were very similar, 0.83 (95% CI 0.61 to 1.12) versus 0.82 (95% CI 0.62 to 1.09).

Secondary outcomes

The three studies also reported unfavourable outcomes. There was no clinically significant difference in the occurrence of these events between participants with or without hypothermia. For details, please refer to [Summary of findings for the main comparison](#).

1. Decompressive craniectomy or corticectomy performed to reduce intracranial pressure during the surgery

No decompressive craniectomy or corticectomy was reported.

2. Newly developed postsurgical vasospasm or infarction during hospitalisation

Thirty-six of 577 (6.2%) participants with hypothermia had postoperative infarction; 40 of 581 (6.9%) participants without hypothermia had infarction. Thirty-four of 577 (6%) participants with hypothermia had clinical vasospasm (temporary deficits); and 32 of the 581 (5.5%) participants without hypothermia had clinical vasospasm.

3. Duration of hospitalisation

None of the studies reported duration of hospital stay.

4. Destination of discharge (home or to another hospital)

Only one study with 112 participants reported discharge destinations ([Hindman 1999](#)). Forty-three of 55 (78.2%) participants with hypothermia were discharged home; 39 of 57 (68.4%) participants in the control group were discharged home. The remaining participants were discharged to other facilities.

5. Postoperative infection of the wound, the lung, the urinary tract, or the skin within one week after surgery.

Thirty-nine of 577 (6.8%) participants with hypothermia had infections; 39 of 581 (6.7%) participants without hypothermia had infections.

6. Cardiac arrhythmia or arrest within one week after surgery

Six of 577 (1%) participants with hypothermia and 6 of 581 (1%) participants without hypothermia had cardiac arrhythmia.

DISCUSSION

Summary of main results

All three studies, with a total of 1158 participants, investigating the effect of intraoperative mild hypothermia for postoperative neurological outcomes, reported better neurological recovery with this treatment, but the statistical estimation of the effect failed to reach certainty.

[Chouhan 2006](#) reported that neurological recovery was better in the hypothermic group (GOS Grade V in 66% versus 47%); [Hindman 1999](#) reported a greater incidence of good long-term outcomes in the hypothermic group (71% versus 57%); and [Todd 2005](#) also reported better recovery in the hypothermia group (GOS grade V in 66% versus 63%).

A random-effects meta-analysis summarising the three RCTs resulted in an estimated risk ratio very close to the recalculated one from the data in [Todd 2005](#), which contributed 1000 of the 1158 included participants and accounted for 85.2% of the weight of the meta-analysis ([Analysis 1.1](#)).

The three included studies also reported unfavourable outcomes; there was no clinically significant difference in the occurrence of these events between participants with and without hypothermia. For details, please refer to [Summary of findings for the main comparison](#).

Overall completeness and applicability of evidence

All three studies examined the effects of intraoperative mild hypothermia, but primarily in people with a good-grade aneurysmal subarachnoid haemorrhage. Postoperative neurological outcomes, quantified by the GOS three months after surgery, were reported by two studies ([Hindman 1999](#); [Todd 2005](#)), the other study followed participants until discharge ([Chouhan 2006](#)). All three studies used good recovery (GOS Grade V) as the indicator for the neuroprotective effect of intraoperative mild hypothermia.

In this review, we focused on postoperative neurological deficits rather than good recovery. In our analysis of the data, we defined people with a GOS Grade 3 or 2 as dependent in activities of daily living; Grade 1 meant death.

Readers should note that the [Chouhan 2006](#) study included all grades of participants, but followed them for less than three months and had missing data. Their data accounted for only 4.9% of the weight of our meta-analysis. So, data for the 13 poor grade participants had little influence on the result. [Chouhan 2006](#) also reported that in subarachnoid haemorrhage Grade II participants, all eight (100%) in the hypothermic group and four out of 10 (40%) in the normothermic group, had good neurological recovery (GOS Grade V). This appears to support the rationale of investigators in [Todd 2005](#), who investigated the effect in good grade participants only.

The other two studies were two stages of one multicentre trial. [Hindman 1999](#), the preliminary stage, included good grade participants and participants without subarachnoid haemorrhage. The second stage of the study, [Todd 2005](#), included only good grade participants and had a large sample size, which carried 85.2% of the weight in our meta-analysis.

Of the 1158 participants included in our meta-analysis, 13 were poor grade while 59 did not have a subarachnoid haemorrhage. Therefore, the result of our meta-analysis basically reflects the effectiveness of intraoperative mild hypothermia on postoperative neurological deficits in people with good grade aneurysmal subarachnoid haemorrhage, not in all people with cerebral aneurysm.

The number of participants without subarachnoid haemorrhage was relatively small in our review. Subgroup analysis on this group would not have reached a conclusion. However, due to its similar clinical scenarios to good grade participants, we speculate that outcomes for this group of people would not be so different.

As the neuro-intensive care field develops, there is a trend to perform surgery or endovascular therapy in the early stage of aneurysmal subarachnoid haemorrhage. Clinically, this implies that more poor grade patients are going to be operated on in some medical centres. Although there was no significant statistical difference in the seven poor grade people who received intraoperative mild hypothermia, we found no clinical evidence to exclude the possibility that this treatment might be effective in this subgroup of people.

The metabolism and autoregulation of the neural or neurovascular system in poor grade people are thought to be under more severe disturbances or damage. We presume this might render the brain or neurovascular system more vulnerable to surgery. In our opinion, the majority of animal models used to investigate the effect of hypothermia for neurological protection are more likely to mimic poor grade people, and they often demonstrate favourable results ([Busto 1987](#); [Busto 1989](#); [Clifton 1991](#); [Dempsey 1987](#); [Dietrich 1990](#); [Minamisawa 1990](#); [Patel 1994](#); [Shimohata 2007](#); [Zhang 1993](#); [Zhao 2007](#)). [Chouhan 2001](#) reported that their preliminary study observed better neurological recovery with intraoperative mild hypothermia in poor grade people, but in [Chouhan 2006](#), a sample size of 13 was obviously not large enough for any conclusion to be drawn with certainty.

Not all the target secondary outcomes were addressed by all of the studies, but complications reported in their separate cohorts were rare, and not attributable to mild hypothermia.

Quality of the evidence

Although data in our analysis were primarily derived from one high-quality study on people with good grade aneurysmal subarachnoid haemorrhage, the overall quality of evidence remains moderate. For those without subarachnoid haemorrhage or those with poor grade subarachnoid haemorrhage, it is inappropriate to make clinical decisions based on these analyses. For secondary outcomes, the ways in which they were reported were so various that the summarised results could only have limited reliability.

Potential biases in the review process

Due to the limited access to all databases, we did not carry out a small fraction of the planned database searches.

Agreements and disagreements with other studies or reviews

We did not find any reviews on the same topic. Although a systematic review of 23 trials on hypothermia for people with

head trauma concluded there was no evidence that hypothermia treatment was effective (Sydenham 2009), no evidence exists to reject a future high-quality trial focusing on intraoperative mild hypothermia for people with poor grade aneurysmal subarachnoid haemorrhage.

AUTHORS' CONCLUSIONS

Implications for practice

In people with good-grade aneurysmal subarachnoid haemorrhage, it remains possible that intraoperative mild hypothermia could prevent death or dependency in activities of daily living. However, the confidence intervals around this estimate include the possibility of both benefit and harm. In people with poor grade aneurysmal subarachnoid haemorrhage or without subarachnoid haemorrhage, there was insufficient information

to allow us to draw any conclusions. We did not identify any reliable evidence to support the routine use of intraoperative mild hypothermia.

Implications for research

A high-quality randomised controlled trial of intraoperative mild hypothermia to prevent post-operative neurological deficits in people with poor-grade aneurysmal subarachnoid haemorrhage appears to be justified.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chouhan 2006

Methods	RCT Single-centre study performed in India
Participants	70 people of either sex, posted for intracranial aneurysm clipping, were included in the study. Participants with severe systemic illnesses, sepsis, peripheral vascular diseases and bleeding disorders were excluded 23 participants were excluded from the data analysis due to failures to achieve target temperature of mild hypothermia (34.5°C to 33°C; N = 11) or normothermia (36.0°C to 37.5°C; N = 12). The data for 47 participants (hypothermia = 24; normothermia = 23) were analysed There was no significant difference in baseline characteristics including: age, sex, body weight, blood pressure
Interventions	Intervention group: mild intraoperative hypothermia of 34.5°C to 33°C, induced and maintained using Polar Air machine cooling and cold intravenous fluids Control: normothermia of 36.0°C to 37.5°C, achieved with the help of Polar Air warming
Outcomes	GOS at discharge Duration of in-hospital stay was not reported Death in each group Intraoperative complications including: brain bulge, hypertensive episodes, premature ventricular contractions, aneurysm rupture, blood loss Immediate postoperative complications including: headache; restlessness; shivering; nausea or vomiting, or both Delayed postoperative complications such as: meningitis, cerebral vasospasm, cerebral infarct
Notes	No funding resource was reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors stated that "All the patients were randomly divided into two groups, to have either (1) Mild hypothermia 'H' (34.5°C to 33.0°C) or (2) nor-

Chouhan 2006 (Continued)

		mothermia 'N' (36.0°C to 37.5°C) at the time of clip application", but the method used for randomisation was not mentioned
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote "The surgical team was blinded to the temperature group assignments". Whether outcome assessors were blinded was not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote "Twenty-three (H = 11; N = 12) patients were excluded from the study, as we could not achieve the target temperature at the time of aneurysm clipping."
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods section were reported
Other bias	Low risk	No suspicion of other bias arose

Hindman 1999

Methods	RCT
	Multentre study at 5 academic medical centres in the US and Canada during the 17-month period between October 1994, and July 1996
Participants	<p>Inclusion criteria: people with intracranial aneurysms (with or without acute SAH) were required to have a pre-hospitalisation/pre-SAH Rankin disability score of 0 or 1. People with acute SAH were required to have a preoperative WFNS score of I, II, or III</p> <p>Exclusion criteria: (1) they were endotracheally intubated when evaluated for study enrolment; (2) they had cryoglobulinaemia, severe Raynaud's disease, sickle-cell disease, or another disorder considered to contraindicate hypothermia; or (3) they were entered in a blinded trial of any drug that could affect neurological outcome; cardiovascular disease was not an exclusion criterion</p> <p>114 people undergoing cerebral aneurysm clipping with (N = 52; WFNS score ≤ III) and without (N = 62) acute aneurysmal SAH were randomised to normothermic (N = 57, target oesophageal temperature at clip application of 36.5°C) and hypothermic (N = 57, target temperature of 33.5°C) groups. 7 hypothermic people (12%) could not be cooled to within 1°C of target temperature; 3 of the 7 were obese</p>
Interventions	<p>Intervention: hypothermic group - the following procedures were used to achieve a target oesophageal temperature of 33.5°C by the time of clip application: (1) the cooling/heating mattress was set to 20°C, (2) the forced air cooling/heating blanket was set to deliver un-warmed (room temperature) air, and (3) intravenous fluids and anaesthetic gases were not warmed</p> <p>Control: normothermic group - the following procedures were used to achieve and maintain a target oesophageal temperature of 36.5°C: (1) the cooling/heating mattress was set to 38°C, (2) the forced air cooling/heating blanket was set to 36 to 38°C, and (3) intravenous fluids and inspired anaesthetic gases were warmed to 37°C</p>
Outcomes	<p>At the time of enrolment, standardised preoperative neurological assessments were conducted. On postoperative days 1, 3, and 7, neurological status was evaluated by a trained examiner who was not aware of group assignment. Both WFNS and NIHSS scores were assigned</p> <p>A final outcome assessment was made using the GOS statistics 3 to 6 months after surgery</p>
Notes	No funding resource was reported

Hindman 1999 (Continued)

Data collecting dates for GOS were not specifically reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "... a previously sealed envelope containing group assignment was opened by the anaesthesiologist ..." but the method used to generate randomised sequence was not reported
Allocation concealment (selection bias)	Low risk	The envelopes were prepared by the co-ordinating centre (University of Iowa)
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote "Group assignment and intraoperative temperature were not revealed to the neurosurgical team during surgery ... On postoperative days 1, 3, and 7, neurological status was again evaluated by a trained examiner who was not aware of group assignment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote "... but three patients without acute SAH were lost to follow-up (all had been assigned to the hypothermia group and were neurologically normal at the time of discharge)."
Selective reporting (reporting bias)	Low risk	Quote "Among patients with acute SAH (N = 52), three in-hospital deaths occurred; one patient in the hypothermic group died on postoperative day 84, and two patients in the normothermic group died on postoperative days 1 and 9, respectively. These deaths were on a neurological basis, resulting either from cerebral infarction or bleeding from another cerebral aneurysm. Both WFNS and NIHSS scores were assigned ... 3 to 6 months after surgery, a final outcome assessment was made using the Glasgow Outcome Scale Statistics."
Other bias	Low risk	No other bias was found

Todd 2005

Methods	RCT Multicentre study from centres in the USA, UK, New Zealand, Austria, Australia, Canada and Germany
Participants	1001 participants with a preoperative WFNS score of I, II, or III (good grade patients), who had SAH no more than 14 days before planned surgical aneurysm clipping: 499 participants were allocated to the hypothermia group, 501 participants were allocated to the normothermia group, and 1 participant was lost to follow-up Inclusion criteria: at least 18 years of age, not pregnant, had suffered a subarachnoid haemorrhage from a radiologically demonstrated intracranial aneurysm within 14 days before surgery, had a WFNS score of I, II, or III ("good grade") at the time of enrolment, which was verified on arrival in the operating room. Participants were required to have had a Rankin score of 0 (no neurologic disability) or 1 (mild disability) before their haemorrhage Exclusion criteria: body-mass index of more than 35, had a cold-related disorder, had an endotracheal tube in place
Interventions	Intervention: participants were assigned to hypothermia, oesophageal temperature was reduced as quickly as possible, without any delay in the progress of surgery. The goal was to achieve a temperature between 32.5 and 33.5° C by the time the first clip was applied Control: the temperature of participants assigned to normothermia was kept between 36 and 37°C

Intraoperative mild hypothermia for postoperative neurological deficits in people with intracranial aneurysm (Review)

Todd 2005 (Continued)

Outcomes	Patients' neurological outcome were assessed 90 days after surgery by means of the GOS, the Rankin scale, the Barthel index, the NIHSS, and a battery of neuropsychological examinations. If a participant could not be seen by examiners at the operating centre, arrangements were made for that participant to be seen elsewhere by a certified examiner
Notes	Study was supported by a grant from the National Institute of Neurological Disease and Stroke (RO1 NS38554)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A permuted-block scheme was used for randomisation, with stratification according to the centre and the time between SAH and surgery (0 to 7 days or 8 to 14 days)
Allocation concealment (selection bias)	Low risk	Less than 2 hours before the planned start of surgery, patients were evaluated and enrolled by means of a telephone-accessed computer system, which directed the anaesthesiologist to use a numbered opaque envelope containing the participant's treatment assignment. The envelope was to be opened only after the induction of anaesthesia
Blinding (performance bias and detection bias) All outcomes	Low risk	All study personnel, except the anaesthesiologists involved in intraoperative care, were unaware of the participants' treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "... resulting in a total enrolment of 1001 patients. One patient was lost to follow-up, leaving 1000 patients in our efficacy population." Comment: 1 participant lost to follow-up out of 1001 participants had little influence on the effect assessment
Selective reporting (reporting bias)	Low risk	Death and neurological outcomes were measured by the GOS, the Rankin scale, the Barthel index, the NIHSS, and the occurrence of possible side effects of this treatment were reported
Other bias	Low risk	No other bias was found

GOS: Glasgow Outcome Score

NIHSS: National Institutes of Health Stroke Scale

RCT: randomised controlled trial

SAH: subarachnoid haemorrhage

WFNS: World Federation of Neurological Surgeons

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baker 1994	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes
Baumgardner 1999	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes
Hinz 2007	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes

Study	Reason for exclusion
Iwata 2006	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes
Karibe 2000	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes
Sato 2000	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes
Steinberg 2001	This study focused on how to achieve hypothermia rather than the therapeutic effects of hypothermia on neurological outcomes
Zhang 2013	Only one author was listed. No information regarding random sequence generation, allocation concealment and blinding was reported

Characteristics of ongoing studies [ordered by study ID]

NCT02544256

Trial name or title	Mild hypothermia during intracranial aneurysm clipping
Methods	Double-blind RCT
Participants	Adults with acute subarachnoid haemorrhage from ruptured aneurysm
Interventions	Participants to be cooled to 33°C after induction for general anaesthesia. Body temperature of 33.8°C to 34.8°C to be maintained up to the end of microcirculation measurement after aneurysm clipping. Body temperature range of 35.8°C to 36.8°C to be maintained in control group
Outcomes	Primary outcome measures: changes in SDF imaging variables 1 and 2 hours after skin incision, brain microcirculation measured by SDF imaging probe Secondary outcome measures: changes in diameter of small brain arteries at operating site, 1 and 2 hours after skin incision measured by SDF probe Other outcome measures: days of hospital stay, GOS on discharge
Starting date	September 2015
Contact information	Tomas Suchy, MD, Email tomas.suchy@fnhk.cz
Notes	This study is estimated to be completed in September 2018

GOS: Glasgow Outcome Score
RCT: randomised controlled trial
SDF: Sidestream Dark Field

DATA AND ANALYSES

Comparison 1. Intraoperative mild hypothermia compared with control (no hypothermia)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency in activities of daily living 3 months post-operatively in all participants	3	1158	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.09]
2 Absolute effect on death or dependency in activities of daily living 3 months post-operatively in all participants	3	1158	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.07, 0.01]

Analysis 1.1. Comparison 1 Intraoperative mild hypothermia compared with control (no hypothermia), Outcome 1 Death or dependency in activities of daily living 3 months post-operatively in all participants. **Analysis 1.2. Comparison 1 Intraoperative mild hypothermia compared with control (no hypothermia), Outcome 2 Absolute effect on death or dependency in activities of daily living 3 months post-operatively in all participants.** **APPENDICES****Appendix 1. MEDLINE (Ovid) search strategy**

1. Intracranial Aneurysm/

Intraoperative mild hypothermia for postoperative neurological deficits in people with intracranial aneurysm (Review)

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2. Aneurysm / or aneurysm, ruptured/
3. Exp brain/ or exp meninges/ or exp cerebral arteries/
4. 3 and 2
5. Subarachnoid hemorrhage/
6. Intracranial hemorrhages/ or cerebral hemorrhage/ or exp basal ganglia hemorrhage/
7. Vasospasm, intracranial/
8. ((intracranial or brain or cerebral or berry or saccular) adj5 aneurysm\$).tw.
9. ((basilar or anterior communicating or posterior communicating or anterior cerebral or middle cerebral or posterior cerebral) adj5 artery adj5 aneurysm\$).tw.
10. ((brain or cerebral or cerebell\$ or intracerebral or intracranial or subarachnoid or arachnoid) adj5 (haemorrhage or hemorrhage or haematoma or hematoma or blood\$ or bleed\$)).tw.
11. ((cerebral or intracranial or cerebrovascular) adj5 (vasospasm or spasm\$)).tw.
12. sah.tw.
13. 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Hypothermia/ or body temperature changes/ or fever/
15. Hypothermia, induced/ or cryotherapy/
16. Exp body temperature/ or exp temperature/ or exp cold temperature/
17. (hypothermi\$ or cold\$ or cool\$ or temperature\$)
18. 14 or 15 or 16 or 17
19. 18 and 13
20. Limit 19 to humans

WHAT'S NEW

Date	Event	Description
17 August 2015	New citation required but conclusions have not changed	The overall results and conclusions remain unchanged.
17 August 2015	New search has been performed	The search was updated to 17 August 2015. We identified two new studies: we excluded one study because the quality was poor, and the other study is ongoing. The number of included studies remains the same: three studies involving 1158 participants. We reformatted the Plain Language Summary and updated the review throughout as appropriate. We did not perform subgroup analyses because there were insufficient data available. We downgraded the quality of the evidence for this review to 'moderate'.

CONTRIBUTIONS OF AUTHORS

Luying Ryan Li searched all databases except the Cochrane Stroke Group Trials Register. Luying Ryan Li and Buwan Chaudary selected and assessed search results. Chao You provided professional interpretation of the results. Luying Ryan Li wrote the manuscript.

DECLARATIONS OF INTEREST

Luying Ryan Li: none known.
Chao You: none known.
Bhuwan Chaudhary: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not search CINAHL and AMED because they were not available to us. In this update, we did not search Chinese Medical Current Contents (CMCC) and Chinese Medical Academic Conference (CMAC) separately, because these two databases have now been combined and incorporated into CNKI and VIP. The Chinese Evidence-Based Medicine Database was unavailable. Google.com was not available in China during this update. We did not find the following additional databases useful: the Chinese Hospital Digital Library (<http://www.chkd.cnki.net/>); Eastview Information Services (http://online.eastview.com/login_china/index.jsp); Science China (http://www.scichina.com/new_web_Fa/index.asp).

We added The WHO International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictcp/en/>) to our searches.

Not all secondary outcomes in the protocol were found in the studies, and we listed all reported secondary outcomes.

In this update, the quality of the evidence for the outcome of death or dependency in activities of daily living in all participants was downgraded to moderate because of imprecision, because the data in our analysis were primarily from people with good-grade aneurysmal subarachnoid haemorrhage.

INDEX TERMS

Medical Subject Headings (MeSH)

Aneurysm, Ruptured [mortality] [*surgery]; Brain Damage, Chronic [mortality] [*prevention & control]; Cerebral Infarction [epidemiology]; Hypothermia, Induced [adverse effects] [*methods] [mortality]; Intracranial Aneurysm [mortality] [pathology] [*surgery]; Intraoperative Care; Postoperative Complications [mortality] [*prevention & control]; Randomized Controlled Trials as Topic; Subarachnoid Hemorrhage [classification] [*complications] [mortality]; Treatment Outcome; Vasospasm, Intracranial [epidemiology]

MeSH check words

Humans