Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review)

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[Intervention Review]

Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation

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ABSTRACT

Background

Good neurologic outcome after cardiac arrest is hard to achieve. Interventions during the resuscitation phase and treatment within the first hours after the event are critical. Experimental evidence suggests that therapeutic hypothermia is beneficial, and a number of clinical studies on this subject have been published.

Objectives

We performed a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were our main outcome parameters. We aimed to perform individual patient data analysis if data were available, and to from subgroups according to the cardiac arrest situation.

Search strategy

We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2007 Issue 1); MEDLINE (1971 to January 2007); EMBASE (1987 to January 2007); CINAHL (1988 to January 2007); PASCAL (2000 to January 2007); and BIOSIS (1989 to January 2007).

Selection criteria

We included all randomized controlled trials assessing the effectiveness of the therapeutic hypothermia in patients after cardiac arrest without language restrictions. Studies were restricted to adult populations cooled with any cooling method applied within six hours of cardiac arrest.

Data collection and analysis

Validity measures, the intervention, outcome parameters and additional baseline variables were entered into the database. Meta-analysis was only done for a subset of comparable studies with negligible heterogeneity. For these studies individual patient data were available.

Main results

Four trials and one abstract reporting on 481 patients were included in the systematic review. Quality of the included studies was good in three out of five included studies. For the three comparable studies on conventional cooling methods all authors provided individual patient data. With conventional cooling methods patients in the hypothermia group were more likely to reach a best cerebral performance categories score of one or two (CPC, five point scale; 1= good cerebral performance, to 5 = brain death) during hospital stay (individual patient data; RR, 1.55; 95% CI 1.22 to 1.96) and were more likely to survive to hospital discharge (individual patient data; RR, 1.35; 95% CI 1.10 to 1.65) compared to standard post-resuscitation care. Across all studies there was no significant difference in reported adverse events between hypothermia and control.

Authors' conclusions

Conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after cardiac arrest. Our review supports the current best medical practice as recommended by the International Resuscitation Guidelines.

PLAIN LANGUAGE SUMMARY

Cooling the body after cardiac arrest

To date about one tenth to a third of successfully resuscitated patients leave hospital to live an independent life again. Clinical studies have shown that this outcome can be improved by cooling the body to about 33°C for several hours after cardiac arrest. We found five randomized trials with data on a total of 481 cardiac arrest survivors. With conventional cooling methods patients were more likely to leave hospital without major brain damage and they were more likely to survive to hospital discharge. No cooling specific adverse events were reported. In summary there is currently evidence supporting the use of conventional cooling to induce mild hypothermia in cardiac arrest survivors within the first hours of restoration of spontaneous circulation.

BACKGROUND

The incidence of out-of-hospital sudden cardiac arrest in industrial countries is reported to be between 0.04% and 0.19% per year (Becker 1993; Rea 2004). Of all patients where resuscitation was attempted, 14% to 40% achieved return of spontaneous circulation and were admitted to hospital (Finn 2001; Fischer 1997; Giraud 1996; Herlitz 2003b; Kuisma 1996; Leung 2001; Rewers 2000). Of those patients admitted to hospital, only between 7% to 30% were discharged from hospital with good neurologic outcome (Absalom 1999; Böttiger 1999; Fischer 1997; Herlitz 1999; Jennings 2001; Westfal 1996; Weston 1997).

Therapeutic hypothermia is still a relatively new concept for the preservation of cerebral function in patients who are resuscitated after cardiac arrest. After patients have been stabilized their body temperature is lowered to 32 to 34°C for a duration of 24 hours. It is believed that therapeutic hypothermia works in multiple ways. Cerebral reperfusion after successful resuscitation, although essential and effective in restoring energy stores, can also trigger harmful chemical cascades. The generation of free radicals and other mediators is responsible for the postresuscitation syndrome, which leads to multifocal damage of the brain (Negovsky 1988). In contrast to accidental hypothermia, therapeutic mild hypothermia (32 to 34°C) is administered in a controlled way. During hypothermia the ability to survive anoxic no-flow states is dramatically increased (Ginsberg 1992). Intra-ischaemic hypothermia for brain protection has been used for several years with certain surgical procedures and circulatory arrest states. Clinical and experimental results show a protective effect of hypothermia during but also after ischaemic situations (Rosomoff 1954). Therapeutic hypothermia can inhibit the biosynthesis, release and uptake of several catecholamines and neurotransmitters (Boels 1985; Okuda 1986) especially glutamate and dopamine, which could lead to tissue damage (Busto 1989; Choi 1987; Globus 1987). Other beneficial effects of hypothermia include the preservation of the blood brain barrier (Karibe 1994), the protection of adenosine triphosphate (ATP) stores (Mizuhara 1996), which are necessary for energy provision; the restitution

of post ischaemic cerebral microcirculation (Takasu 1996), and possibly also decreased intracranial pressure and increase cerebral blood flow (Marion 1997). Subsequently, hypothermia reduces the amount of cell death in certain brain regions (Busto 1989b) and seems to act in a multifactorial way by influencing several damaging pathways simultaneously.

Postresuscitation care has developed many new concepts in the past few years aiming at improving neurological outcome and survival of patients after cardiac arrests. It comprises optimizing haemodynamics and ventilation, electrolytes, seizure control, temperature and glucose control and is summarized in the main resuscitation guidelines (AHA 2000; ERC 2005).

Recently, two randomized controlled trials (RCTs) showed that induced hypothermia has a neuro protective effect in patients who are primarily resuscitated from cardiac arrest (Bernard 2002; HACA 2002). A meta-analysis pooled the data of these two RCTs and the data of one additional feasibility study and showed a clear benefit in terms of neurologic outcome and survival with hypothermia treatment for patients successfully resuscitated after cardiac arrest (Holzer 2005). Although recommended in the guidelines of the International Liaison committee on Resuscitation (ILCOR) (Nolan 2003) and the recent resuscitation guidelines (ERC 2005), therapeutic hypothermia still is a relatively new concept. At the moment many different cooling methods exist: conventional cooling comprises extracorporeal methods with cooling pads, ice packs, water immersion or intravascular cooling with cooling catheters or simply cold fluids. Cooling can also be combined with haemofiltration or any extracorporeal cardiopulmonary support. Studies with different treatment modalities are emerging and therefore systematic and regular updates of the literature are important to monitor new and effective developments. We undertook this Cochrane review with a view to assembling the current literature.

OBJECTIVES

We aimed to perform a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were our main outcome parameters. We aimed to perform individual patient data analysis if data were available. We intended to form subgroups according to the cardiac arrest situation.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and "quasi randomized", controlled trials. "Quasi randomized" refers to allocation procedures such as alternating days, odd and even days, and the like.

Types of participants

We included studies in adult patients who suffered from cardiac arrest (regardless of in-hospital or out-of-hospital cardiac arrest) and were successfully resuscitated.
We excluded studies on children and adolescents (aged less than 18 years) as the presumed cause of cardiac arrest is different to those in adults.
Although patients with a prior neurologic history may not greatly benefit from the intervention, we did not exclude them for the following reasons:

1. the number of such patients most likely is negligible; and
2. in a real life situation information on neurological performance before the arrest is often not available when starting post-resuscitation therapy.

Types of interventions

The intervention of interest was therapeutic hypothermia, regardless of how body temperature was reduced, applied within six hours of arrival at hospital. We defined therapeutic as any body target temperature below 35°C. We defined the control intervention as treatment according to the standard treatment after cardiac arrest at the time of the trial.

Types of outcome measures

Primary outcomes

The primary outcome measure was neurological recovery. Ideally we expected the outcome to be reported as best neurologic outcome during hospital stay and in cerebral performance categories (CPC) (Cummins 1991; Jennett 1975). The CPC categories are defined as follows.

1. Good cerebral performance: conscious, alert, capable of normal life. Normal cerebral function. May have minor psychological or neurological deficits, which do not significantly compromise cerebral or physical function.
2. Moderate cerebral disability: conscious, alert, sufficient cerebral function for activities of daily life (e.g. dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.
3. Severe cerebral disability: conscious, has at least limited cognition. Dependant on others for daily life support (i.e., institutionalized or at home with exceptional family effort),

because of impaired brain function. Includes wide range of cerebral abnormalities, from ambulatory patients who have severe memory disturbance or dementia precluding independent existence, to paralysed patients who can only communicate with their eyes (e.g. the locked-in syndrome).

4. Coma/vegetative state: not conscious, unaware of surroundings, no cognition. No verbal and/or psychological interaction with environment. May appear awake because of spontaneous eye opening or sleep-wake cycle. Includes all degrees of unresponsiveness, which are neither CPC three (conscious) nor CPC five (coma, which satisfies brain death criteria).

5. Certified brain death.

If authors grouped this outcome into one or two (good recovery), and three to five (unfavourable recovery) we adapted it for our meta-analysis. If not reported in CPC categories we accepted when authors reported "good" neurologic outcome, which we assumed to be comparable with CPC score of one or two.

Secondary outcomes

Survival to hospital discharge, survival at six months and long-term, quality of life at six months and long-term, dependency, and cost-effectiveness. We defined long-term as a minimum of one year.

Adverse events

We aimed at reporting adverse events as given by the authors.

Search methods for identification of studies

We searched the following databases for relevant published trials: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2007 Issue 1); MEDLINE (1971 to January 2007); EMBASE (1987 to January 2007); CINAHL (1988 to January 2007); PASCAL (2000 to January 2007); and BIOSIS (1989 to January 2007). We did not apply any language restrictions. In an attempt to identify further studies we asked experts in the field whether they were aware of any ongoing, unpublished, or published trials on this subject. We performed the searches entering search terms as multiple postings (.mp, term appears in the title, abstract or MeSH) and some as medical subject headings (MeSH) for MEDLINE and exploded terms for EMBASE and CINAHL (search terms for CENTRAL, Appendix 1; MEDLINE, Appendix 2; EMBASE, Appendix 3; CINAHL, Appendix 4; BIOSIS and PASCAL, Appendix 5).

A search strategy for identifying RCTs was used with MEDLINE (Dickersin 1994) and EMBASE (Lefebvre 1996).

The search was completed on 25 January 2007.

Data collection and analysis

Data extraction

We independently extracted data using a data extraction form (see Appendix 6).We imported all retrieved results into EndNote (version 7.0, Thomson Corporation) and eliminated duplicates. Two authors (JA, MH) independently scanned each reference for inclusion in the review. As we intended to use original individual patient data of the identified trials we contacted the respective corresponding author and asked for collaboration. Two authors independently entered all relevant data into The Cochrane Collaboration's software program Review Manager (RevMan 5). We compared the two versions and resolved disagreements by discussion. To assess the internal validity of the identified trials, we assessed allocation sequence generation, allocation concealment, blinding of outcome assessment, exclusion of randomized patients from the analysis, comparability of groups, and loss to follow up.

The following variables were entered into RevMan 5:

1. allocated intervention;

2. event (best neurological recovery during hospital stay, survival to hospital discharge);

3. additional baseline variables: cause of cardiac arrest (presumed cardiac versus non-cardiac); location of arrest (in-hospital versus out-of-hospital); witnessed versus non-witnessed arrest; primary ECG rhythm (ventricular fibrillation versus other).

Quantitative data synthesis

We assessed data for clinical and statistical heterogeneity. We only performed quantitative synthesis of the data if clinical heterogeneity was negligible. Clinical heterogeneity may be caused by differences in study populations, interventions or definitions of the endpoint (Thompson 2001). In case of severe heterogeneity it may not be suitable to pool the data because the trials measure a different effect altogether.

Analysis at the individual level

Quantitative analysis of individual patient data was intended when studies had negligible heterogeneity and individual patient data was available at least for a clinically comparable subset. In the case that individual patient data were unavailable for at least one study, we planned to do an analysis at the study level. This applies in particular to further updates. We performed quantitative analysis of individual patient data using standard statistical procedures provided in RevMan 5. We calculated relative risks and their 95% confidence intervals. All analyses were according to the intention-to-treat principle. The principal measure of effect was the relative risk of achieving good neurological recovery defined as a best CPC

category of one or two or the definition which was given by the author for "good neurologic outcome".

Analysis at the study level

Here also the principal measure of effect was the relative risk of achieving good neurological recovery in patients allocated to hypothermia when compared to those not receiving hypothermia at hospital discharge. In case of negligible statistical heterogeneity we used fixed-effect models to calculate summary effects, otherwise we used random-effects models. Statistical heterogeneity was assessed using the I^2 statistic (Higgins 2003). Statistical heterogeneity was considered relevant if I^2 was > 50%.

Subgroup analyses

For the primary endpoint we formed subgroups using the individual patient data according to the following variables:

- cause of cardiac arrest (presumed cardiac versus non-cardiac);
- location of arrest (in-hospital versus out-of-hospital);
- witnessed versus non-witnessed arrest;
- primary ECG rhythm (ventricular fibrillation versus other)

Sensitivity analysis

We performed sensitivity analyses for the impact of study quality issues as measured by allocation concealment on the overall effect estimate and the effect size of all identified trials neglecting heterogeneity and publication status.

Publication bias

We assessed the presence of possible publication bias and heterogeneity using funnel plots (plotting the effect against precision) (Egger 1997).

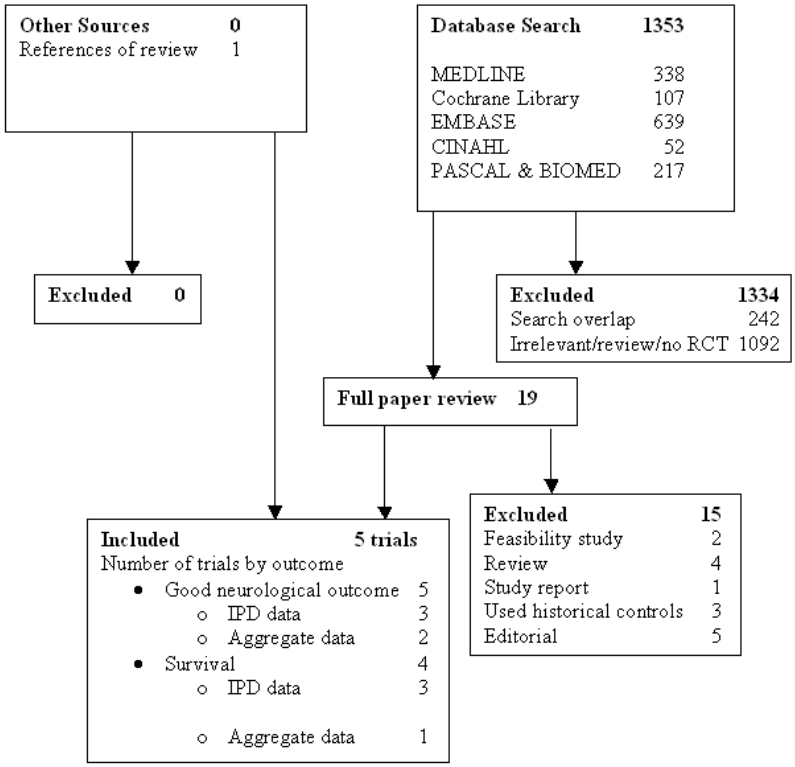
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Our systematic search of databases of the medical literature resulted in 1353 hits. From those we excluded 242 duplicates;1092 further papers were excluded according to our eligibility criteria (randomized studies on adult cardiac arrest patients treated with therapeutic hypothermia, neurologic recovery as outcome) by judging the abstract or the title. Nineteen papers remained for closer inspection. From those we excluded two feasibility studies, four studies that were reviews, one report on the published RCTs of therapeutic hypothermia after cardiac arrest, three studies that used historical controls, and five studies that turned out to be comments or editorials (see Characteristics of excluded studies and Figure 1).

Figure 1. Searching results



Looking through the references of a recently published systematic review on therapeutic hypothermia (Cheung 2006) we found one additional reference, published only as abstract (Mori 2000). Hence five randomized and quasi-randomized controlled trials with a total of 481 patients remained for analysis (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Mori 2000, see Characteristics of included studies).

Clinical heterogeneity

We identified clinical heterogeneity due to cooling methods. In contrast to the other studies, Laurent 2005 used haemofiltration as mode of cooling which is substantially different to the standard cooling methods used in the other RCTs. As the cooling method of Mori 2000 was unclear, we presented this study separately and did not pool the effect with those of the remaining studies. For the three comparable studies on conventional cooling methods all authors provided individual patient data (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001).

Risk of bias in included studies

We assessed each included trial by the following criteria: mode of randomization, allocation concealment, level of blinding, loss to follow up, comparability of groups and use of measures to account for differences between groups. Quality of the included studies was good in three out of five studies. Three trials (HACA 2002; Hachimi-Idrissi 2001; Laurent 2005) reported adequate randomization methods and the use of opaque envelopes to conceal treatment allocation. Three trials reported blinded outcome assessment (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001). One study lost information for two patients for the primary endpoint (HACA 2002). All other studies had a complete follow-up. In two studies treatment and control group did not differ significantly in reported baseline characteristics (Hachimi-Idrissi 2001; Laurent 2005) while one of these had rather small groups (Hachimi-Idrissi 2001). In HACA 2002 there were some baseline differences between groups. Patients in the normothermia group were more likely to have a history of diabetes mellitus or coronary heart disease and to have received basic life support from a bystander than were those in the hypothermia group. The authors adjusted for all baseline variables and the risk ratio increased slightly, from 1.40 (95% confidence interval (CI) 1.08 to 1.81) to 1.47 (95% CI 1.09 to 1.82). Bernard 2002 reported differences in sex and rate of

bystander cardiopulmonary resuscitation between groups but did not further adjust for this possible bias. Mori 2000 did not provide information on baseline characteristics of the patient groups.

Effects of interventions

Primary outcome

Good neurologic outcome

With only three studies reporting on conventional cooling methods (involving 195 cases and 188 controls), the pooled result showed better survival for the hypothermia group (individual patient data; RR, 1.55; 95% CI 1.22 to 1.96; I^2 = 32%; see Analysis 1.1.1).

As there was only one study for patients undergoing haemofiltration after cardiac arrest (Laurent 2005), it was not possible to employ meta-analysis. Using the data in the study, however, and carrying out a chi-squared statistic we found no statistical difference (Pearson chi^2 statistic = 0.16 P = 0.69; RR, 0.71; 95% CI 0.32 to 1.54; see Analysis 1.1.2).

The one study reporting on an unknown cooling method (Mori 2000) showed better survival for the hypothermia group (Pearson chi^2 = 7.78, P = 0.005; RR, 4.50; 95% CI 1.17 to 17.30; see Analysis 1.1.3.).

Secondary Outcomes

Survival to hospital discharge

With only three studies reporting on conventional cooling methods (involving 195 cases and 188 controls), the pooled result showed better survival for the hypothermia group (individual patient data; RR, 1.35; 95% CI 1.10 to 1.65; I^2= 0%; see Analysis 2.1.1).

As there was only one study for patients undergoing haemofiltration after cardiac arrest (Laurent 2005) the chi^2 statistic found that there was no statistical difference (Pearson chi^2 = 0.77, P = 0.38; RR, 0.71; 95% CI 0.32 to 1.54; see Analysis 2.1.2).

Survival at 6 months and long-term

We found no data on this outcome.

Quality of life at 6 months and long-term dependency

We found no data on this outcome.

Cost effectiveness

We found no data on this outcome.

Subgroup Analyses

According to the number of patients and information provided by the authors we formed subgroups of the meta-analysis by the following parameters: cause of cardiac arrest (presumed cardiac versus non-cardiac), location of arrest (in-hospital versus out-of-hospital); witnessed versus non-witnessed arrest, primary ECG rhythm (ventricular fibrillation (VF/VT) versus other). The endpoint was "best ever reached CPC during hospital stay" (see Additional Table 1).

Table 1. Subgroup Analyses

Outcome or Subgroup	Studies	Participants	Risk Ratio (M-H, Fixed, 95% CI)
Good neurological outcome by cardiac cause vs non-cardiac cause	3	383	1.54 [1.22, 1.95]
Cardiac cause	3	372	1.51 [1.19, 1.91]
Non-cardiac cause	2	11	3.80 [0.55, 26.29]
Good neurological outcome by location of cardiac arrest	3	382	1.56 [1.23, 1.98]
In-hospital	1	17	1.64 [0.47, 5.73]

Table 1. Subgroup Analyses (*Continued*)

Out-of-hospital	3	365	1.56 [1.23, 1.99]
Good neurological outcome by witnessed cardiac arrest	3	382	1.49 [1.18, 1.88]
Witnessed cardiac arrest	3	360	1.43 [1.13, 1.81]
Non-witnessed cardiac arrest	3	22	5.31 [1.40, 20.21]
Good neurological outcome by primary ECG rhythm	3	382	1.51 [1.19, 1.91]
VF/VT rhythm	2	330	1.47 [1.15, 1.88]
Non- VF/VT rhythm	2	52	2.17 [0.68, 6.93]

- The effect size for patients with a cardiac cause (three studies) and VF/VT was nearly the same (two studies)

- Groups of patients with non-VF/VT rhythm as first cardiac rhythm (n = 52), and patients with a non-cardiac cause (n = 11), and in-hospital arrests (n = 17) were small and did not show a statistically significant effect (non-VF/VT: RR 2.17; 95% CI 0.68 to 6.93; I^2= 50%; two studies; non-cardiac cause RR 3.80; 95% CI 0.55 to 26.29; I^2= 0%; two studies; in-hospital: RR, 1.67; 95% CI 0.47 to 5.73)

- Also a small number of patients had non-witnessed arrest (n = 22). Among these patients the effect size was substantially bigger than the summary effect for the whole study population (RR 5.31; 95% CI 1.40 to 20.21; I^2= 0%; three studies)

- For patients with witnessed cardiac arrest the effect size was slightly smaller than the effect size for the whole study population (RR 1.43; 95% CI 1.13 to 1.81; I^2= 0%; three studies)

Long-term outcome, cost-effectiveness, and quality of life

None of the retrieved studies provided data on long term survival and dependency, quality of life, or cost-effectiveness.

Adverse events

We included all trials that reported on adverse events in the analysis, regardless of heterogeneity. The following adverse events were reported in the four studies: bleeding of any severity, need for platelet transfusions, pneumonia, sepsis, pancreatitis, renal failure or oliguria, haemodialysis, pulmonary oedema, seizures, lethal or long lasting arrhythmias, cardiac complications, hypocalcaemia, and hypophosphataemia. There were no significant differences between the groups (see Additional Table 2).

Table 2. Adverse Events

Outcome or Subgroup	Studies	Participants	Risk Ratio (M-H, Fixed, 95%CI)
Bleeding of any severity	1	273	1.38 [0.88, 2.16]
Need for platelet transfusion	1	273	5.11 [0.25, 105.47]
Pneumonia	1	273	1.27 [0.90, 1.78]
Sepsis	1	273	1.93 [0.89, 1.78]
Pancreatitis	1	273	0.51 [0.05, 5.57]

Table 2. Adverse Events (*Continued*)

Renal failure or oliguria	2	303	0.88 [0.48, 1.61]
Haemodialysis	2	350	1.11 [0.41, 3.01]
Pulmonary edema	1	273	1.76 [0.61, 5.12]
Seizures	1	273	0.89 [0.39, 2.02]
Lethal or long lasting arrhythmia	2	315	1.21 [0.88, 1.67]
Pressure sores	1	273	Not estimable
Significant haemorrhagic complications	1	77	Not estimable
Cardiac complications	1	77	0.16 [0.01, 3.21]
Hypokalaemia	1	42	0.91 [0.31, 2.68]
Hypophosphataemia	1	42	1.12 [0.65, 2.25]

Sensitivity Analysis

Does allocation concealment influence the effect?

For studies using conventional cooling methods, cooling had a favourable effect on good neurological outcome in studies with adequate allocation concealment. This effect, however, was significant in a fixed-effect model (RR 1.50; 95% CI 1.16 to 1.93; see Additional Table 3) but not significant in a random-effects model (RR 1.97; 95% CI 0.71, 5.45). This result comes from two studies which showed both a significant and positive effect, but there was statistical heterogeneity (I^2 = 59%), and total sample size comprised only 306 patients.

Table 3. Sensitivity Analysis

Outcome or Subgroup	Studies	Participants	Risk Ratio (M-H, Fixed, 95%CI)
Good neurological outcome all studies	5	479	1.55 [1.24, 1.94]
Studies with conventional cooling and adequate allocation concealment	2	306	1.50 [1.16, 1.93]

Table 3. Sensitivity Analysis (*Continued*)

Studies with conventional cooling and inadequate or unknown allocation concealment	1	77	1.84 [0.97, 3.49]
Studies with other cooling methods and adequate allocation concealment	1	42	0.71 [0.32, 1.54]
Studies with other cooling method and inadequate or unknown allocation concealment	1	54	4.50 [1.17, 17.30]

As we were concerned that model choice might influence our results we also examined whether this might cause changes in our main effect as a post hoc sensitivity analysis. The effect for conventional cooling as presented in Analysis 1.1.1 did not change by model choice (fixed-effect RR 1.55; 95% CI 1.22 to 1.96; random-effects RR 1.64; 95% CI 1.10 to 2.45; data not shown). This indicates that the effect is robust according to model choice.

Does allowing for clinical heterogeneity and publication status affect the results?

When we ignored clinical heterogeneity and publication status the pooled effect of all studies did not change substantially, whether fixed-effect models (RR 1.55; 95% CI 1.24 to 1.94; Table 3), or random-effects models (RR 1.68; 95% CI 1.00 to 2.68; data not shown) were used.

Publication bias

At the moment there are too few studies to draw inferences from funnel plots, we have therefore not presented them in the current version of this review.

DISCUSSION

Quality of evidence

We found five studies on the application of mild hypothermia with a total of 481 patients (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005; Mori 2000). All studies were academia initiated. Quality of the studies was generally good. Except for the abstract (Mori 2000), all studies reported on almost all essential quality criteria and loss to follow up was within an acceptable range. One study could have done better on the randomization process and the adjustment for inequalities in baseline characteristics between the treatment and the control group (Bernard 2002). After our literature search we were able to include the data of all eligible studies we retrieved. It was not possible to obtain individual patient data for Laurent 2005 or Mori 2000, but even if they had been available we would not have included either study in the meta-analysis. In the case of Laurent 2005 the two treatment modalities (mild therapeutic hypothermia with or without haemodialysis) are clinically too heterogeneous to be combined. As mentioned in the background section, one of the theories of the beneficial effects of cooling deals with attenuation of the effect of free radicals and other mediators. Haemofiltration may act in a similar way by reducing the numbers of free radicals. It may add to the effect of therapeutic hypothermia or even supersede the effect of therapeutic hypothermia. In the case of Mori 2000 we do no know anything about the treatment.

All studies planned to include consecutive patients (no information available on Mori 2000). In HACA 2002 10% and in Bernard 2002 8% of all eligible patients were not randomized because of logistic problems or because the next of kin did not give consent. In Laurent 2005 and Hachimi-Idrissi 2001 inclusion of all eligible patients was reported. We do not have any information on the patients that were not randomized.

In HACA 2002 hypothermia was discontinued in 14 patients because of death, arrhythmia, haemodynamic instability, technical problems with the cooling device, one liver rupture, one previous, random assignment to the hypothermia group, one error in the duration of cooling. These patients were included in the intention-to-treat analysis of primary and secondary outcome. One patient in each group was lost to follow up for the primary outcome. All other studies had a complete follow-up.

The control groups differed with regard to fever control. Mean

body temperature 12 hours after start of cooling in the "normothermia group" was around 37.6°C in HACA 2002 and 37.4°C in Bernard 2002. Hachimi-Idrissi 2001 did not report on the body temperature of the control group. It is known that for each degree rise in temperature over 37 degrees Celsius, the risk of an unfavourable neurologic outcome increases, with an odds ratio of 2.26 (Zeiner 2001). If this is true even for smaller temperature differences, the beneficial effect of therapeutic hypothermia might at least partly be due to an antipyretic rather than a hypothermic effect. It is questionable whether a strict temperature control would have the same effect as mild hypothermia - as shown in a study of fever control in patients in a neurologic intensive care unit, where no difference in outcome was found with fever control (Diringer 2001).

For the primary data analysis, individual patient analysis gave the same results as study-based results. We still made the effort to obtain individual patient data as it was useful for investigating the subgroups.

All studies with individual patient data reported on the same outcome and all outcome assessors were blind to the treatment (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001; Laurent 2005).The cerebral performance category (CPC) is easy to measure and gives a crude approximation of the patient's ability to perform tasks of the daily life. One of its limitations is the lack of accuracy when it comes to estimating cognitive functions, personal and social impacts of cardiac arrest.

For the subgroup of patients with non-witnessed arrests we observed an effect size substantially bigger than the pooled summary effect (RR, 5.31; 95% CI 1.40 to 20.21; Table 1). However, the group of non-witnessed arrests was small (22 patients only) and yielded large confidence intervals. Although it seems that patients benefit from the treatment, the result should be interpreted with caution.

One of the problems with merging the data for this review was the difference in the inclusion criteria. Generally among all patients that are resuscitated and brought to hospital, between 18% and 42% have non-witnessed arrests, only 30% to 58% a confirmed VF rhythm as first rhythm (Herlitz 2003a; Haukoos 2004; Kim 2001), 40% of all resuscitations happen in hospital. In this review the two bigger studies included only patients with cardiac cause of cardiac arrest, and with VF/VT-rhythm as first cardiac rhythm (Bernard 2002; HACA 2002). Most of these patients had out-of-hospital cardiac arrest. From the pathogenesis of global cerebral ischaemia and the theories as to why therapeutic hypothermia is effective, there is no reason why therapeutic hypothermia should not be as effective in patients with asystole as first cardiac rhythm or non-cardiac causes for cardiac arrest. In a meta-analysis (Holzer 2005) the effect of therapeutic hypothermia was only sightly changed by baseline variables. A retrospective cohort study showed that the effect of therapeutic hypothermia was independent of various confounders including cardiac arrest conditions (Arrich 2006).

The major limitation of this review is the small number of randomized controlled trials and hence small numbers of included patients. Therefore the precision of our effects is generally low, and particularly in subgroup and sensitivity analyses this is a matter for concern. The confidence intervals of the intervention come near the null difference and looking at studies with adequate allocation concealment resulted in an effect which was not robust to model choice in our sensitivity analysis. On the other hand only two studies have been included in the sensitivity analysis which is probably too small to make firm conclusions. Nonetheless, given these limitations the effect of conventional cooling methods consistently points towards a favourable neurological outcome. Another consequence of the small number of available studies are the many single study comparisons.

One might argue that therapeutic hypothermia is only available to countries with sufficient financial resources. But there are many cooling methods ranging from expensive device controlled methods to very cheap cold fluids and ice packs which are available in all facilities where post-resuscitation care is performed. Proof of superiority of any cooling method above others is still lacking, and there are currently no formal cost-benefit analyses.

Main results

Our review shows that therapeutic hypothermia with conventional cooling methods improves neurologic outcome and survival of patients successfully resuscitated after cardiac arrest. Currently available evidence suggests that patients with out-of-hospital cardiac arrest, a presumed cardiac cause of cardiac arrest and for patients with a VF/VT rhythm as first recorded cardiac rhythm benefit from therapeutic hypothermia. For patients with in-hospital cardiac arrest, asystole and non-cardiac causes of arrest the group sizes are too small to make firm inferences. There were no statistically significant differences in any of the reported adverse events between hypothermia and non-hypothermia patients.

What does this review contribute?

After the publication of the two RCTs on therapeutic hypothermia, (Bernard 2002; HACA 2002) guidelines by the International Liaison Committee on Resuscitation (ILCOR) on the application of therapeutic hypothermia after cardiac arrest were published (Nolan 2003). Despite a small number of included trials and patients the results of our review support those recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

Conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after

cardiac arrest. Our review supports the current best medical practice as recommended by the International Resuscitation Guidelines.

Implications for research

Future research should be done with standardized temperature monitoring (either oesophagus or bladder temperature measurements) in order to be able to compare between groups and between studies at a later stage. Effective measures need to be advanced to cool the patient to the target temperature within a short time period which should decrease heterogeneity within the study population. For studies with a focus on out-of-hospital cooling, practical methods need to be evaluated. To further investigate the effect of cooling on subgroups, like patients with a non-VF/VT as primary cardiac rhythm, or patients with in-hospital cardiac arrest, methodologically sound studies are needed. There is a knowledge gap concerning an optimal cooling protocol. For this purpose inclusion criteria should be widened and comparisons of earlier cooling (pre-hospital) versus late cooling (in-hospital), different levels of hypothermia (e.g. 32°C versus 34°C), and different durations of cooling (e.g. 12 hours versus 24 hours versus 48 hours) should be included. Safety reporting should not only comprise the known but any unexpected adverse events. It would be useful to include cost benefit analyses in future studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bernard 2002

Methods	Randomization: pre-hospital
Participants	Total number of patients 77, mean age of 66 years, 33% female. Out-of-hospital cardiac arrest of cardiac cause, ventricular fibrillation as first cardiac rhythm, comatose after resuscitation Participating sites: Australian university and community hospitals. Multicenter: yes Language: English Allocation concealment: not applicable (odd and even days) Outcome assessor blind: yes Intention-to-treat: yes Groups comparable: more females and more bystander CPR in hypothermia group Follow-up > 80% of randomized patients: yes
Interventions	Therapeutic hypothermia versus standard pre hospital treatment protocols and intensive care treatment Means of cooling: packs placed around the head, neck, torso, and limbs Cooling rate: time from ROSC to target temperature: two hours Target temperature: 33°C Duration of cooling: 12 hours after target temperature was reached Rewarming: passive after 12 hours, active after 18 hours
Outcomes	Survival with good neurologic function to be sent home or to a rehabilitation facility at discharge. In-hospital death Haemodynamic, biochemical, and hematologic effects of hypothermia. For IPD analysis best ever reached CPC during hospital stay and CPC discharge were provided.
Notes	Randomization: odd and even days

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Odd and even days
Allocation concealment?	No	Odd and even days
Blinding? All outcomes	Yes	Outcome assessment blinded
Incomplete outcome data addressed? All outcomes	Yes	Complete follow-up

Bernard 2002 (*Continued*)

Free of other bias?	Yes	No other major biases seen

HACA 2002

Methods	Randomization: in hospital
Participants	Total number of patients 275, mean age 59 years, 24% female In and out-of-hospital bystander-witnessed cardiac arrest of presumed cardiac cause, ventricular fibrillation or non perfusing ventricular tachycardia as first cardiac rhythm, comatose after resuscitation. Participating sites: European university and community hospitals. Multicenter: yes Language: English Allocation concealment: opaque envelopes Outcome assessor blind: yes Intention-to-treat: yes Groups comparable: significantly more diabetes and coronary heart disease and bystander CPR in control group. Follow-up > 80% of randomized patients: yes
Interventions	Therapeutic hypothermia versus standard intensive care treatment Means of cooling: cooling blanket that covered the whole body and released cooled air Cooling rate: time from ROSC to target temperature: median of 8 hours Target temperature: 32 to 34°C Duration of cooling: median of 24 hours Rewarming: passive over eight hours
Outcomes	Best CPC of 1, 2 versus CPC of 3, 4, 5 during six months Mortality at six months, rate of complication during first seven days after cardiac arrest (bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores) For IPD analysis best ever reached CPC during hospital stay and CPC discharge were provided.
Notes	Randomization: computer generated random sequence

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	

HACA 2002 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Two patients lost to follow up, properly addressed.
Free of other bias?	Yes	

Hachimi-Idrissi 2001

Methods	Randomization: in hospital
Participants	Total number of patients 33, mean age 72 years, 39% female Out-of-hospital cardiac arrest of cardiac cause, asystole as first cardiac rhythm, comatose after resuscitation Participating site: Belgian university hospital. Multicenter: no Language: English Outcome assessor blind: yes Intention-to-treat: yes Groups comparable: yes, although groups were small, no significant difference Follow-up > 80% of randomized patients: yes
Interventions	Therapeutic hypothermia versus standard post resuscitation care protocol Means of cooling: helmet device placed around the head and neck and containing a solution of aqueous glycerol Cooling rate: starting point until target temperature not clearly stated Target temperature: 34°C Duration of cooling: Start of cooling to start of rewarming: mean three hours Rewarming: passive over eight hours
Outcomes	Haemodynamic data, arterial pH, electrolytes, haematological data Complications such as pneumonia, sepsis, cardiac arrhythmia, coagulopathy Survival to hospital discharge and overall performance categories (OPC) For IPD analysis best ever reached CPC during hospital stay and CPC discharge were provided.
Notes	Randomization: random number tables IPD included 33 patients, the article only reported on 30 as the follow-up was not completed at the time of submission

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	

Hachimi-Idrissi 2001 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Difference between published report and IPD properly reported
Free of other bias?	Yes	

Laurent 2005

Methods	Randomization: pre-hospital
Participants	Total number of patients 42, mean age 52 years in the HF group, 56 years in the HF+HT group, 19% female Out-of-hospital cardiac arrest of presumed cardiac cause, ventricular fibrillation or asystole as first cardiac rhythm, comatose after resuscitation. Participating sites: French university and community hospital. Multicenter: yes Language: English Allocation concealment: opaque envelopes Outcome assessor blind: not stated Intention-to-treat: yes Groups comparable: yes Follow-up > 80% of randomized patients: yes
Interventions	High-flow haemofiltration versus high-flow haemofiltration plus therapeutic hypothermia versus standard supportive care Means of cooling: direct external cooling of the blood Cooling rate: four hours after ICU admission the median temperature was 31.7°C Target temperature: 32 to 33°C Duration of cooling: 24 hours Rewarming: passive
Outcomes	Survival at six months Rate of death by intractable shock in patients who had a favourable Glasgow coma scale (M5 or M6) or required sedation Survival at CPC 1, 2 versus all else at six months
Notes	Randomization pre-hospital to save time for HF We did not pool data from this study with data from the three other studies, since the treatment schemes with haemofiltration are not comparable to non-haemofiltration treatment (clinical heterogeneity).

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	

Laurent 2005 (*Continued*)

Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	
Free of other bias?	Yes	

Mori 2000

Methods	Randomization: unknown
Participants	Total number of patients 54, mean age unknown, gender distribution unknown Out-of-hospital cardiac arrest of unknown cause with a Glasgow Coma Scale of less than eight. Participating site: Japanese university hospital Multicenter: unknown Language of abstract: English Allocation concealment: unknown Outcome assessor blind: not stated Intention-to-treat: unknown Groups comparable: unknown Follow-up > 80% of randomized patients: yes
Interventions	"Brain-hypothermic treatment" versus "brain normothermic treatment" Means of cooling: unknown Cooling rate: unknown Target temperature: 32 to 34°C Duration of cooling: three days Rewarming: unknown
Outcomes	Glasgow outcome scale at one month (5 point scale). The categories "moderate, mild, or no disabilities" were defined as "good neurologic outcome"
Notes	Only abstract published Study was not included in the pooled analysis as we did not have any information on the cooling method, whether cooling was applied locally or systemically, and whether cooling was successful. Attempts to contact the authors were unsuccessful.

CPR=cardiopulmonary resuscitation
ROSC=restoration of spontaneous circulation
CPC=cerebral performance categories
HF=haemofiltration
ICU=intensive care unit
M5=localizes painful stimuli
M6=obeys commands

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

Ballew 2002	Comment
Bernard 1997	Controlled study, historical controls
Bernard 2004	Review
Callaway 1997	Review
Callaway 2002	Feasibility study
Chanin 2002	Editorial
Ebell 2002	Comment
Gwinnutt 2003	Editorial
Kitamura 1989	Feasibility study
Mayer 2002	Clinical trials report
Smith 2002	Review
Ungerleider 1998	Review
Ungerleider 2004	Comment
Yanagawa 1998	Controlled study, historical controls
Zeiner 2000	Controlled study, historical controls

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

Kim 2007

Methods	Randomization: pre-hospital, block randomization
Participants	Total number of patients 125, mean age 67 years in the field cooling group, 65 years in the control group, 19% female Out-of-hospital cardiac arrest, nontraumatic, age > 17, return of pulse, tracheal intubation, intravenous access, oesophageal temperature probe, comatose after resuscitation, ventricular fibrillation or asystole as first cardiac rhythm, oesophageal temperature not lower than 34°C. Participating sites: 7 acute care hospitals in Seattle. Multicenter: yes

Kim 2007 (*Continued*)

	Language: English Allocation concealment: opaque envelopes Outcome assessor blind: no Intention-to-treat: yes Groups comparable: yes Follow-up > 80% of randomized patients: yes
Interventions	In-field cooling versus in-field standard care. Means of cooling: infusing up to 2 L of 4°C normal saline Cooling rate: 1.24 °C Target temperature: not defined Duration of cooling: until arrival at hospital Rewarming: passive
Outcomes	Temperature change, various safety data, deaths before hospital admission, in-hospital deaths, ever awakening, days to awakening, days to death.
Notes	The aims of the study were to assess the feasibility, safety, and effectiveness of in-field cooling.

Tiainen 2007

Methods	Randomization: in hospital
Participants	Total number of patients 70, mean age 59 years in the hypothermia group, 55 years in the control group, 13% female. Patients randomized into the Hypothermia After Cardiac Arrest (HACA) trial (HACA 2002) (in and out-of-hospital bystander-witnessed cardiac arrest of presumed cardiac cause, ventricular fibrillation or non perfusing ventricular tachycardia as first cardiac rhythm, comatose after resuscitation) and surviving for at least 3 months were included. Participating sites: university hospital. Multicenter: no Language: English Allocation concealment: opaque envelopes Outcome assessor blind: yes Intention-to-treat: yes Groups comparable: yes Follow-up > 80% of randomized patients: yes
Interventions	Therapeutic hypothermia versus standard intensive care treatment Means of cooling: cooling blanket that covered the whole body and released cooled air Cooling rate: time from ROSC to target temperature: median of 8 hours Target temperature: 32 to 34°C Duration of cooling: median of 24 hours Rewarming: passive over eight hours
Outcomes	Neuropsychological examinations, quantitative electroencephalography, and auditory P300 event-related potentials at three months after cardiac arrest. Cerebral performance categories 3 and 6 months after cardiac arrest, Mini Mental State Examination at day 14, mortality at six months.

Tiainen 2007 (*Continued*)

Notes	Study was a sub-study of the HACA-trial (HACA 2002).

DATA AND ANALYSES

Comparison 1. Neurological Outcome: cooling vs. no cooling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Good neurological outcome	5	479	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.24, 1.94]
1.1 Conventional cooling without extracorporal methods (IPD, best ever reached CPC of 1 or 2 during hospital stay)	3	383	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.22, 1.96]
1.2 Cooling with haemofiltration (no IPD, CPC of 1 or 2 at six months)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.32, 1.54]
1.3 Unknown method (no IPD, Glasgow Outcome scale of 1-3 at one month)	1	54	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [1.17, 17.30]

Comparison 2. Survival: cooling vs. no cooling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Conventional cooling without extracorporal methods (IPD, survival to discharge)	3	383	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.10, 1.65]
1.2 Cooling with haemofiltration (no IPD, six-months survival))	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.32, 1.54]

WHAT'S NEW

Last assessed as up-to-date: 24 January 2007.

29 October 2009	Amended	Typo corrected in co-author's address (Müllner)

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Harald Herkner (HH), Michael Holzer (MH), Marcus Müllner (MM)

Co-ordinating the review: HH, MM

Undertaking manual searches: MH, Jasmin Arrich (JA)

Screening search results: MH, JA

Organizing retrieval of papers: JA

Screening retrieved papers against inclusion criteria: MH, JA, MM

Appraising quality of papers: MH, HH, JA, MM

Abstracting data from papers: MH, JA

Writing to authors of papers for additional information: MH

Providing additional data about papers: MH

Obtaining and screening data on unpublished studies: MH, JA

Data management for the review: JA, MM

Entering data into Review Manager (RevMan 5): MH, JA

RevMan statistical data: HH, MM, JA

Other statistical analyses not using RevMan: HH, MM

Double entry of data: MH, JA

Interpretation of data: MH, HH, JA, MM

Statistical inferences: HH, MM, JA

Writing the review: JA, MM, HH

Securing funding for the review: not applicable

Performing previous work that was the foundation of the present study: MM, MH

Guarantor for the review (one author): JA

Person responsible for reading and checking review before submission: HH

DECLARATIONS OF INTEREST

The Medical University of Vienna received an unrestricted scientific grant from Alsius Corporation for an independent scientific project, which was used for financing the post of Jasmin Arrich.

Michael Holzer received travel grants for scientific conferences from Alsius Corporation and Kinetic Concepts, Inc (KCI) and honoraria for lectures from Medivance and KCI. He is member of the scientific advisory board of KCI.

Marcus Müllner and Michael Holzer were involved in the design, conduct and publication of the HACA 2002 trial.

Harald Herknerno conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Medical University of Vienna, Austria.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol we aimed to include additional endpoints like the six months and final CPC score, long-term mortality, quality of life at six months, long-term dependency, and cost-effectiveness. The retrieved studies did not provide any information on long-term mortality and dependency, quality of life, or cost effectiveness.

All studies that were included in the individual patient analysis provided data on both best and final neurologic outcome (Bernard 2002; HACA 2002; Hachimi-Idrissi 2001). In our opinion the "best neurological score during hospital stay" is superior to the final score as the final score may be influenced by other factors like worsening of body functions or re-arrests.

Bernard 2002 and Hachimi-Idrissi 2001gave information on survival to hospital discharge, HACA 2002 additionally on the six-months survival, Laurent 2005 only gave information on the six-months survival. As the study by Laurent was not included in the individual patients analysis we chose survival to hospital discharge as a secondary endpoint for the individual patient analysis.

The documentation of adverse effects were overlooked in the original protocol. As they form a vital part of every review we included them in the data extraction sheet before we performed the literature search.

In accordance with our reviewers to better explain the reasons for dual analysis and the way it was carried out we have changed the wording of the objectives from:

"The aim of this study is to present a systematic review of the literature and, if applicable, a meta-analysis, concerning the neuroprotective effect of induced hypothermia in primary cardiac arrest survivors. We plan to use data at the aggregate (study) level and the individual (patient) level."

to:

"We aimed to perform a systematic review and meta-analysis to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. Neurologic outcome, survival and adverse events were our main outcome parameters. We aimed to perform individual patient data analysis if data were available. We intended to form subgroups according to the cardiac arrest situation."

The title has been changed from "Hypothermia for neuroprotection after cardiopulmonary resuscitation" to "Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation".

INDEX TERMS

Medical Subject Headings (MeSH)

*Cardiopulmonary Resuscitation [adverse effects]; Brain Diseases [*prevention & control]; Heart Arrest [*complications; therapy]; Hypothermia, Induced [*methods]; Randomized Controlled Trials as Topic; Recovery of Function

MeSH check words

Adult; Humans