Mild induced hypothermia after out-of-hospital cardiac arrest

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Background

The brain of a patient resuscitated after cardiac arrest (CA) may have suffered ischemia and when the spontaneous circulation is re-established, the subsequent reperfusion may cause further damage [1]. Brain ischemia and the reperfusion injury lead to tissue degeneration and loss of neurological function, to an extent which is dependent on duration and density of the ischemia. Temperature control and mild induced hypothermia (MIH) (33-36°C) mitigate this damage in the experimental setting [2-6] and clinical trials have shown promising results in improving neurological function and survival [7, 8]. Since 2005 MIH has been included in post-resuscitation guidelines from the European Resuscitation Council and the American Heart Association [9, 10] but to our knowledge this has not been done after doing a high quality systematic review with thorough evaluation of the available evidence including level of bias, degree of risk of random error, and possible design errors.

Description of the condition

In Europe around 300.000 inhabitants suffer out-of hospital cardiac arrest (OHCA) yearly [11]. Mortality after OHCA is high and for patients hospitalised alive, the survival rate has been reported to vary between 34 and 56% [12-14]. Further, the frequency of persistent neurological deficits varies considerably [12, 14-18]. At admittance to hospital the body temperature of resuscitated OHCA patients is reported to be around 36°C [19, 20], but it is then gradually rising. Elevated body temperature is common during the first 48 h after CA [21, 22] and is associated with worse outcome [19]. The post-resuscitation period was previously regarded as the missing link in the chain of survival [23], but during the last years this has changed. Research has focused on the use of temperature control with MIH, but the general care of CA patients has also been improved with standardised active intensive care [24] and attention to coronary reperfusion and circulatory support [25, 26].

Description of the intervention

MIH is instituted on CA patients who are unconscious after return of spontaneous circulation (ROSC). Patients are mechanically ventilated, sedated and when necessary paralysed with neuromuscular blocking agents to reduce shivering and subsequent heat-generation and energy consumption [7]. The core body temperature is lowered as quickly as possible to a predefined target temperature with ice-cold intravenous solutions [27], ice-packs [8, 28] and commercially available cooling devices [29]. The target temperature is then maintained between 12 and 48 hours, with the vast majority being treated for 24 hours. After the maintenance period core temperature is gradually raised to normothermia.

How the intervention might work

The post-ischemic period is complicated by hyperthermia induced by generation of pyrogens in the brain but also hyperthermia secondary to infection. Fever occurring during the first 48 hours after global ischemia may be detrimental and is in considerable disfavour of an optimal cerebral metabolic rate of oxygen ($CMRO_2$) [30]. Bringing temperature to normothermia diminishes brain damage in the experimental setting [31]. The developement of ischemic neuronal damage is a complex process, involving mutiple mechanisms acting synergistically or in series. After an early contribution of excitotoxicity and free radical oxidative stress, inflammation, calcium imbalance, modification of gene transcription and apoptosis appear to contribute to damage in experimental models [1]. MIH with decreased body and brain temperature, effectively diminishes brain damage in animal models of cardiac arrest ischemia [2-6]. The protective action of mild hypothermia is equally multifactorial affecting multiple detrimental mechanisms [32] which may account for its efficacy as a protective treatment: lowered cell metabolism, diminished exitotoxicity, less calcium overload, less inflammation, modified gene expression and anti-apoptosis. Altogether, the efficacy of MIH in the experimental setting is pronounced and clinical trials have shown promising results in cardiac arrest patients [7, 8] as well as in neonatal asphyxia [33, 34].

Why it is important to do this review

The translation of MIH treatment into clinical practice is supported by sound experimental data. The results from two clinical trials have changed current guidelines and MIH is now recommended as a treatment for adult OHCA patients who are unconscious when resuscitated after a primary cardiac rhythm of ventricular fibrillation or tachycardia [9, 10]. Guidelines also have an addendum that MIH might be beneficial for in-hospital cardiac arrests and for cardiac

arrest with other primary rhythms [10]. However, there are no references to support this latter statement. The implementation of MIH varies between countries and continents and in many places MIH is not utilised [35-38]. In surveys physicians state lack of firm evidence, lack of resources and too technically difficult among others as reasons for not implementing MIH [36, 39]. There has been criticism of the rapid inclusion of MIH into clinical gudielines [40-42]. However, when read carefully, the guidelines conclude that further studies to support MIH are essential [10]. The objective of this study is to evaluate if there is equipoise to perform another clinical study, randomising to normothermia and MIH, or if the evidence of today is sufficient to support full implementation of MIH -treatment into clinical practice.

Objectives

The objective of this review is to systematically evaluate the level of evidence for therapeutic hypothermia as an intervention to improve survival and neurological outcome after cardiac arrest in the adult population. We will perform meta-analyses and a Trial Sequential Analysis.

Methods

Criteria for considering studies for this review

Types of studies

Randomised clinical trials will be included in the review. We will also explore the intervention effect in quasi randomized studies, cohort studies, and case-control studies.

Types of participants

Adult patients resuscitated from cardiac arrest

Types of interventions

Induced mild hypothermia to a level of 32-35°C compared to no temperature intervention..

Types of outcome measures

Primary outcome

1.Mortality recorded at maximal follow-up.

Secondary outcome

2. Neurological function at maximal follow-up using e.g. the Cerebral Performance Category Scale (CPC) [43]: CPC 1-conscious, no neurological disability; CPC 2-conscious, moderate neurological disability, can work; CPC 3-conscious, severe neurological disability, dependent; CPC 4-coma or vegetative state; CPC 5-dead. The outcome may be dichotomised to Good Outcome (CPC 1-2) and Bad outcome (CPC 3-5) and other outcome measures of neurological outcome may also be applicable. Neurological outcome should be recorded at hospital discharge or preferably at 6-12 months.

Search methods for identification of studies

Electronic searches

The following sources will be included in the literature search to identify relevant trials:

The Cochrane Library CENTRAL, MEDLINE and EMBASE until February 2009.

The overall search strategy will combine searches for cardiac arrest and mild induced hypothermia with searches for randomised controlled trials. The planned searches are listed in full in the appendix. (with the following key words: hypothermia, therapeutic hypothermia, induced hypothermia, mild hypothermia, cardiac arrest, OHCA, resuscitation, cardiopulmonary resuscitation, neurological function, survival. Randomised Controlled Trials will be identified manually.)

We will also search ongoing trials using the following databases:

- Current Controlled Trials (www.controlled-trials.com).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- Centre Watch Clinical Trials Listing Service (www.centerwatch.com).
- International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch).

Searching other resources

Experts in the field of mild induced hypothermia from Europe, North-America, Australia and Asia will be asked for their knowledge of ongoing or unpublished studies. We will also hand search reference lists of retrieved RCTs and reviews on MIH.

Data collection and analysis

Selection of studies

Publications will be rejected unless two of the authors (NN and JW) from the initial search can determine with certainty from the title and abstract that the trial has been done exclusively or predominantly in patients after cardiac arrest, is not a randomised clinical trial, or is not comparing MIH with control treatment. If we are not able to reject with certainty a publication on the basis of title and abstract the full text of the article will be obtained.

Studies will be retrieved to assess if the study; (i) compares MIH with no temperature intervention; (ii) includes patients after cardiac arrest;

A flow diagram of the numbers of studies identified and rejected at each stage will be prepared in accordance with PRISMA-guidelines [44].

Data extraction and management

Two authors (NN and JW) will independently extract information on each trial using standard data extraction forms. The forms include data concerning trial design, participants, interventions, and outcomes as detailed in the selection criteria described above (for details see 'Characteristics of included studies', Table 1, and Appendix 2). Any relevant missing information will be sought from the original author(s) of the article if required.

Differences between authors will be resolved by discussion and involvement of a third author (CG).

Assessment of risk of bias in included studies

Bias will be assessed according to each domain of bias according to the Cochrane Handbook. Studies will be regarded as having low-risk of bias if all of the following criteria are fulfilled: adequate generation of allocation sequence, adequate allocation concealment, adequate blinding and analysis performed by intention to treat. We are aware of the inherent problems with blinding of MIH -treatment and we will consider blinding adequate if the outcome assessors have been blinded to type of intervention (allocation group).

Methodological quality is defined as the confidence that the design and the report of the randomised clinical trial will restrict bias in the comparison of the intervention [45]. According to empirical evidence, the methodological quality of the trials is based on sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias [45-51].

Since there is no sufficiently well designed formal statistical method to combine the results of studies at high and low risk of bias, the major approach to incorporating risk of bias assessments in Cochrane reviews is to *restrict* meta-analysis to studies at low (or lower) risk of bias [48]. Two authors (NN and JW) will independently assess the risk of bias in each trial. Any differences of opinion will be resolved through discussion with CG.

Quality components are classified as follows:

Sequence generation

Low risk of bias, if the allocation sequence is generated by a computer or random number table or similar.

Uncertain risk of bias, if the trial is described as randomised, but the method used for the allocation sequence generation was not described.

High risk of bias, if a system involving dates, names, or admittance numbers are used for the allocation of patients (quasi-randomised). Such trials will be excluded.

Allocation concealment

- Low risk of bias, if the allocation of patients involves a central independent unit, on-site locked computer, or consecutively numbered, sealed envelopes.
- Uncertain risk of bias, if the trial is described as randomised, but the method used to conceal the allocation is not described.
- High risk of bias, if the allocation sequence is known to the investigators who assigned participants or if the study is quasi-randomised. Such trials will be excluded.

Blinding

It is not possible to blind the health-care provider and patients in the treatment groups. Blinding is considered adequate if the outcome assessors are blinded, although we are aware of the fact that even such trials may be subject to bias.

- Low risk of bias, if the outcome assessors are blinded and the method of blinding is described.
- Uncertain risk of bias, if the outcome assessors are blinded and the method of blinding is not described.
- High risk of bias, if the outcome assessors are not blinded.

Incomplete data outcomes

- Low risk of bias, if there are no post-randomisation drop-outs or withdrawals.

- Uncertain risk of bias, if it is not clear whether there are any drop-outs or withdrawals or if the reasons for these drop-outs are not clear.
- High risk of bias, if the reasons for missing data are likely to be related to true outcomes, 'as-treated' analysis is performed, potentially inappropriate application of simple imputation, potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.

Selective outcome reporting

- Low risk of bias, if all the important outcomes are reported or if the trial's protocol is available and all of the trial's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- Uncertain risk of bias, if there is insufficient information to assess whether the risk of selective outcome reporting is present.
- High risk of bias, if not all the pre-specified outcomes are reported or if the primary outcomes are changed or if some of the important outcomes are incompletely reported.

Baseline imbalance

- Low risk of bias, if there was no baseline imbalance in important characteristics.
- Uncertain risk of bias, if the baseline characteristics were not reported.
- High risk of bias, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Early stopping

- Low risk of bias, sample size calculation is reported and the trial is not stopped or the trial is stopped early by a adequate stopping rule.
- Uncertain risk of bias, if sample size calculations are not reported and it is not clear whether the trial is not stopped early.
- High risk of bias, if the trial is stopped early without formal stopping rules.

Sponsor bias

- Low risk of bias, if the trial is without funding or is not funded by an instrument or equipment or drug manufacturer.
- Uncertain risk of bias, if the source of funding is not clear.
- High risk of bias, if the trial is funded by an instrument or equipment or drug manufacturer.

Academic bias

- Low risk of bias, if the author of the trial has not conducted previous trials addressing the same interventions.
- Uncertain risk of bias, if it is not clear if the author has conducted previous trials addressing the same interventions.
- High risk of bias, if the author of the trial has conducted previous trials addressing the same interventions.

The influence of individual quality criteria will be explored in a sensitivity analysis.

Measures of treatment effect

Primary outcome will be neurological function according to defenition above with the longest follow-up data from each trial.

Dichotomous data

Data on dichotomous outcomes will be statistically summarised as relative risks (RR) with 95% confidence intervals (CI).

Continuous data

Continuous outcomes will be summarised as difference in means (MD) with 95% CI and an overall MD will be calculated in the meta-analysis. For studies addressing the same outcome but using different outcome measures (for example different scales measuring quality of life) mean differences (MD) will be used.

Time-to-event data

Time-to-event outcomes (for example time until death) will be expressed as hazard ratios (HR) with 95% CI.

Unit of analysis issues

Dealing with missing data

We will attempt to find out missing data by contacting the trial authors and the impact of any missing data will be discussed. Evaluation of randomised patients in intention-to-treat and per protocol populations will be performed.

When using meta-analysis for combining results from several studies with binary outcomes (i.e., event or no event), adverse side effects may be rare but serious and hence important [52]. Most

meta-analytic software does not include trials with zero events in both arms (intervention versus control) when calculating RR. Exempting these trials from the calculation of RR and CI may lead to overestimation of a treatment effect. In case of trials with zero event in both arms, we will perform a sensitivity analysis by applying *empirical continuity corrections* to these trials as proposed by Sweeting et al. by applying an imaginary mortality of 0.001 in both arms [53, 54].

Intention-to-treat analysis is recommended in order to minimise bias in design, follow-up and analysis of the efficacy of randomised clinical trials. It estimates pragmatic the benefit of a change in treatment policy rather than the potential benefit in patients who receive the treatment exactly as planned [55]. Full application of intention-to-treat is possible when complete outcome data are available for all randomised participants. Despite the fact that about half of all published reports of randomised clinical trials state that intention-to-treat is used, handling of deviations from randomised allocation varies widely and many trials have missing data on the primary outcome variable [55]. The methods used to deal with deviations from randomised allocation are generally inadequate, potentially leading to bias [55].

Performing an intention-to-treat analysis in a systematic review is not straightforward in practice since reviewers must decide how to handle missing outcome data in the contributing trials [56]. No consensus exists about how missing data should be handled in intention-to-treat analysis, and different approaches may be appropriate in different situations [48, 55].

In case of missing data we will apply '*complete-case analysis*' for primary and secondary outcomes, which simply excludes all participants with the missing outcome from the analysis as well as 'worst-best' and 'best-worst' scenario analyses. Additionally, if possible we will conduct a sensitivity analysis for primary and secondary outcomes by applying the '*uncertainty method*'. This method is an ad hoc approach that decreases the weight given to trials with missing data.

The weight of the trials is based on the amount of information contained in each trial, taking into consideration both the sampling error and the potential impact of the missing data [56].

Dealing with duplicate publications

If we identify more than one publication of an original trial, we will assess those articles together to maximise data collection. In case of substantial disagreements between older and newer articles the authors will be contacted.

Assessment of heterogeneity

A priori the authors will evaluate clinical diversity of the included trials. Heterogeneity will be identified by visual inspection of the forest plots, by using a standard ?2-test with a significance level of P = 0.1. Heterogeneity will be specifically examined with I^2, where I^2 values of 50 % and more indicate a substantial level of heterogeneity [48]. When heterogeneity is found, we will attempt to determine potential reasons for it by examining individual trial characteristics and those of subgroups of the main body of evidence.

Clinical heterogeneity will be assessed by comparing the trials with regard to different clinical variables: **patient characteristics, duration of disease, glycaemic target, and outcome**. When significant clinical, methodological or statistical heterogeneity is found, we will survey the individual trial in trying to determine potential reasons for it.

We plan to use both a random-effects model [57] and a fixed-effect model [58]. In case of discrepancy between the two models we report both results. Otherwise, we will report only the fixed-effect model.

Between-trial heterogeneity will be explored by meta-regression depending on the data available.

Assessment of reporting biases

Funnel plots will be used to provide visual assessment whether effects are associated with trial size. There are a number of reasons for the asymmetry of a funnel plot (for example methodological design of trials and publication bias) [48].

Data synthesis

Data will be summarised statistically if they are available and of sufficient quality. Statistical analysis will be performed according to the statistical guidelines in the newest version of The Cochrane Handbook for Systematic Reviews of Interventions [48].

Trial sequential analysis

Trial sequential analysis (TSA) is a methodology that combines an information size calculation (cumulated sample sizes of included trials) for meta-analysis with the threshold of statistic significance. TSA is a tool for quantifying the statistical reliability of data in cumulative meta-analysis adjusting P-values for repetitive testing on accumulating data. TSA will be conducted on the primary outcomes and on the secondary outcomes if possible [59-61].

Meta-analysis may result in type I errors due to systematic errors (bias) or random errors due to repeated significance testing when updating meta-analysis with new trials [59, 61]. Bias from trials with low methodological quality, outcome measure bias, publication bias, early stopping for benefit, and small trial bias may result in spurious P-values [59, 61].

In a single trial, interim analysis increases the risk of type I errors. To avoid type I errors, group sequential monitoring boundaries are applied to decide whether a trial could be terminated early because of a sufficiently small P-value, that is the cumulative Z-curve crosses the monitoring boundaries [62]. Sequential monitoring boundaries can be applied to meta-analysis as well, called trial sequential monitoring boundaries. In TSA the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed.

The idea in TSA is that if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials are needed. If the Z-curve does not cross the boundary then there is insufficient evidence to reach a conclusion. To construct the trial sequential monitoring boundaries the information size is needed and is calculated as the least number of participants needed in a well-powered single trial [59, 61, 63, 64]. We will apply TSA since it prevents an increase of the risk of type I error (< 5%) due to potential multiple updating in a cumulative meta-analysis and provides us with important information in order to estimate the level of evidence of the experimental intervention. Additionally, TSA provides us with important information regarding the need for additional trials and the required information size.

We will apply trial sequential monitoring boundaries according to an heterogeneity-adjusted information size based on an intyervention effect suggested by all included trials and the trials with low bias risk employing alfa = 0.05 and ß =0.20.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed mainly if one of the primary outcome measures demonstrates statistically significant differences between intervention groups. In any other case

subgroup analysis will be clearly marked as hypothesis generating exercise. The following subgroup analyses are planned:

- According to low-risk or high risk of bias
- Duration of the intervention.
- Temperature level of the intervention
- Adjuvant interventions
- Age groups.
- In hospital or out hospital cardiac arrests
- Type of cardiovascular disease at baseline of trials.
- Test of interaction will be applied to determine effect of subgroup on intervention effect.

Sensitivity analysis

We will perform sensitivity analysis in order to explore the influence of the following factors on effect size:

- Repeating the analysis taking the main risk of bias domains of studies into account.
- Repeating the analysis including studies with zero events in treatment groups with TSA program applying an empirical continuity correction of 0.01 for zero events[54].
- Repeating the analysis excluding unpublished trials.

The robustness of the results will also be tested by repeating the analysis using different measures of effects size (relative risk, odds ratio etc.) and different statistical models (fixed- and random-effects models).

For the meta-regression we will consider the covariates for the subgroup analysis.

Results

Discussion

Authors' conclusions

Contributions of authors

NIKLAS NIELSEN: Development of the initial idea for the review, development of protocol, undertaking of searches, selection of studies, data extraction, quality assessment of studies, data analysis, contact person, development of final review.

HANS FRIBERG: Assessment of clinical validity, development of final review.

CHRISTIAN GLUUD: Development of protocol, advisement on statistical methods to be used, development of final review.

JOHAN HERLITZ: Assessment of clinical validity, development of final review.

JØRN WETTERSLEV: Proposal of the review, development of protocol, advisement on statistical methods to be used, data extraction, quality assessment of studies, data analysis, development of final review.

Data extraction sheet

	Trial 1	***Trial 2***	***etc***
Name of principal author/ investigator			
Year of publication			
Duration of trial			
Type of publication, journal, study			
Number of participating sites			
Description of the participants/ population			
Adequate generation of the allocation sequence			
Adequate allocation concealment			
Blinded assessment of primary outcome			

Blinded assessment of secondary outcome			
Baseline imbalance			
Selective outcome reporting			
Intention-to treat (ITT) analyses done			
Intention-to treat (ITT) analyses possible			
Early stopping/ sample size for power analysis reported			
Other biases (industry, academic etc.)			
Description of the Intervention			
Control intervention			
Level of TH (ºC)			
Duration of TH (hours)			
Inclusion criteria			
Exclusion criteria			
Outcomes: Primary, secondary, tertiary			
Number of patients screened			
Number of patients randomised			
Number of patients treated per protocol (intervention/ control)			
Number of patients lost to follow-up			
Median age (years IQR)			
Male sex (%)			
Follow up time			
Survival outcome			
Number of patiens that died in the observation period with the intervention			
Number of all patients in the intervention group			
Number of patiens that died in the observation period in the control group			
Number of all patients in the control group			
Neurological outcome			
Good outcome intervention			
Number of all patients in the intervention group			
Good outcome control			
Number of all patients in the control group			
Tertiary outcome (define)			
Outcomes with the intervention			
Number of all patients in the intervention group			
Outcome with the control intervention			
Number of all patients in the control group			
Management of body temperature in control group			
Reported temperature in control group			
Key conclusion			
Comments by authors in article			
Comments by reviewer			

Characteristics of studies

	Trial 1	*Trial 2*	*etc*
Duration of study (months)			
Participants			
Experimental intervention			
Control intervention			
Inclusion criteria			
Exclusion criteria			
Follow up time			
Patients screened (n)			
Patients included (n)			

Summary of findings tables

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Appendices

Search strategy

Terms for data base search
1) Randomized clinical trials 2) Cardiac arrest OR out of hospital cardiac arrest OR OHCA OR in hospital cardiac arrest OR IHCA OR circulatory arrest OR heart stop OR resuscitation OR cardiopulmonary resuscitation OR CPR 3) Hypothermia OR therapeutic hypothermia OR induced hypothermia OR mild hypothermia OR temperature control OR temperature management OR thermoregulatory management OR thermoregulatory control OR chill therapy OR cooling OR body temperature 4) Neurological function OR neurological recovery OR neurological outcome OR cerebral performance category

OR CPC OR survival OR outcome OR temperature OR ischemia OR brain ischemia OR cerebral ischemia OR global ischemia
5) Humans
1) AND 2) AND (3) OR 4)) AND 5)

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