Hypothermia for neuroprotection after cardiac arrest: Systematic review and individual patient data meta-analysis

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Objective: **Only a few patients survive cardiac arrest with favorable neurologic recovery. Our objective was to assess whether induced hypothermia improves neurologic recovery in survivors of primary cardiac arrest.**

Data Source: **Studies were identified by a computerized search of MEDLINE, EMBASE, CINAHL, PASCAL, the Cochrane Controlled Trial Register, and BIOSIS.**

Study Selection: **We included randomized and quasi-randomized, controlled trials of adults who were successfully resuscitated, where therapeutic hypothermia was applied within 6 hrs after arrival at the emergency department and where the neurologic outcome was compared. We excluded studies without a control group and studies with historical controls.**

Data Extraction: **All authors of the identified trials supplied individual patient data with a predefined set of variables.**

Data Synthesis: **We identified three randomized trials. The analyses were conducted according to the intention-to-treat principle. Summary odds ratios were calculated using a random effects model and translated into risk ratios. More patients in the hypothermia group were discharged with favorable neurologic recovery (risk ratio, 1.68; 95% confidence interval, 1.29–2.07). The 95% confidence interval of the number-needed-to-treat to allow one additional patient to leave the hospital with favorable neurologic recovery was 4–13. One study followed patients to 6 months or death. Being alive at 6 months with favorable functional neurologic recovery was more likely in the hypothermia group (risk ratio, 1.44; 95% confidence interval, 1.11–1.76).**

Conclusions: **Mild therapeutic hypothermia improves short-term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research. (Crit Care Med 2005; 33:414–418)**

KEY WORDS: ventricular fibrillation; asystole; hypoxia-ischemia; brain; reperfusion injury; hypothermia

The incidence of out-of-hospital sudden cardiac arrest in industrial countries ranges from 0.04 to 0.13% of the total population per year (1, 2). Of those patients admitted to the hospital, only 11–48% will be discharged from the hospital with good neurologic outcome (3–17).

For successful resuscitation with favorable neurologic recovery, it is important not only to stop the ischemia process caused by cardiac arrest as fast as possible but also to overcome the following postresuscitation syndrome (18, 19), which consists of four different damaging pathomechanisms: a) perfusion failure (multifocal no-reflow, transient global hyperemia with delayed, prolonged global and multifocal hypoperfusion) (20); b) reoxygenation injuries (oxygen free radicals, invasion of inflammatory cells, electron conduction defects in injured mitochondria, and an increase of excitatory amino acids) (21–23), which could lead to primary necrosis (24, 25) and/or triggering of programmed cell death (apoptosis) (21, 26); c) extracerebral causes (postanoxic viscera) (27); and d) blood derangement during stasis in cardiac arrest (28).

Clinical and experimental results show a multifactorial neuroprotective effect of hypothermia during and after ischemic situations by simultaneously influencing several damaging pathways (23, 29–40).

Recently, two trials showed that induced hypothermia has a neuroprotective effect in patients who could be primarily resuscitated from cardiac arrest (41, 42). We therefore undertook a systematic review of the literature and performed an individual patient data meta-analysis of all identified trials. We looked at the therapeutic effect of induced hypothermia in survivors of primary cardiac arrest.

MATERIALS AND METHODS

We searched for trials where therapeutic hypothermia (any target temperature $<35°C$) was applied within 6 hrs after arrival at the emergency department. We included randomized and quasi-randomized, controlled trials in adult survivors of cardiac arrest. We ex-

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cluded studies without a control group and studies with historical controls.

We searched MEDLINE, EMBASE, CINAHL, PASCAL, the Cochrane Central Register of Controlled Trials, and BIOSIS from 1990 until November 2002. We used a filter to identify randomized controlled trials, a filter for the intervention, and a filter for the condition. No language restrictions were applied. We also scanned the references of relevant studies and reviews. To identify unpublished studies, the principal investigators of the three randomized trials were asked whether they knew of any other randomized trials in this area.

The primary outcomes of interest were short-term outcome and long-term outcome. Favorable short-term outcome was defined as good neurologic recovery and discharge from the hospital. Favorable long-term outcome was defined as good neurologic recovery and being alive 6 months after the event. Good neurologic recovery was defined as "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" or better. This is, according to the cerebral performance categories (CPC) (43, 44), a CPC score of 1 or 2.

To assess the internal validity of trials identified, we assessed allocation sequence generation, allocation concealment, and blinded outcome assessment.

All principal authors of the identified trials agreed to supply individual patient data. Analyses were according to the intention-to-treat principle. The principal measure of effect was the relative risk of favorable short-term and long-term outcome in patients with hypothermia compared with patients without induced hypothermia. We used random effects logistic regression and generalized linear mixed models to analyze individual patient data (45). A detailed description of the modeling procedure used can be provided on request.

RESULTS

Systematic Review of the Literature. Our systematic search of databases of the medical literature resulted in 991 hits. After we excluded hits referring to other treatment modalities than hypothermia or other diseases than resuscitation from cardiac arrest and articles not containing original data, seven controlled studies remained. Three studies used historical controls (46–48), and four trials were randomized and quasi-randomized (41, 42, 49, 50). One trial (50) was excluded because it investigated whether application of hypothermia during advanced cardiac life support was feasible.

Characteristics of Included Trials. We identified three relevant trials where hypothermia was applied after primarily successful resuscitation (41, 42, 49). One trial involved nine centers in five European countries where 275 patients were enrolled (41). Comatose survivors of witnessed ventricular fibrillation cardiac arrest of presumed cardiac origin were randomized to standard or mild hypothermia therapy (target bladder temperature 32–34°C) for 24 hrs. Hypothermia was applied by means of a blanket that covered the whole body and released cooled air. The random sequence was computer generated and concealed by using opaque envelopes. Outcome assessors were blinded to the intervention. Two patients were lost to neurologic follow-up.

One trial involved four centers in Australia where 77 patients were enrolled (42). Comatose survivors after ventricular fibrillation cardiac arrest were included. Patients were assigned to mild hypothermia on odd days and regular treatment on even days. Hypothermia was applied by means of ice packs placed around the head, neck, torso, and limbs. The target pulmonary artery temperature was 33°C and was maintained until 12 hrs after arrival. The outcome assessor was blinded to the intervention.

The third trial took place in one of the centers also participating in the European multiple-center study (49). As the inclusion criteria were different, none of the patients were included in more than one trial. The published article only reports on 30 patients. Here we report on 33 patients, as follow-up was not completed at the time of submission. In this trial, comatose survivors of cardiac arrest with a primary electrocardiographic rhythm of asystole or pulseless electrical activity were enrolled. Systemic hypothermia was achieved with a helmet device placed around the head and neck and containing a solution of aqueous glycerol. The patients were cooled to a target bladder temperature of 34°C for a maximum of 4 hrs. The random sequence was generated with random number tables, and treatment allocation was concealed by using opaque envelopes. Outcome assessors were blinded to the intervention.

All principal investigators provided individual patient data for the meta-analysis. Clinical characteristics are presented in Table 1.

Short-Term Effects of Hypothermia. In all three studies, patients were followed until death or hospital discharge, whichever occurred first. Patients in the hypothermia group were more likely to be discharged with no or only minimal neurologic damage (risk ratio, 1.68; 95% confidence interval, 1.29–2.07; Table 2). This translates to a number-needed-to treat of 6 (95% confidence interval, 4–13). The intracluster correlation coefficient of this model was .04 (95% confidence interval, .005–.21, $p = .04$). We also repeated the analysis after redefining good neurologic recovery as CPC 1 only ("conscious, alert, sufficient cerebral function for activities of daily life"). The effect of hypothermia remained unchanged (1.64, 1.25–2.05).

Controlling for the baseline variables age, gender, and time from collapse to return of spontaneous circulation did not influence the effect (1.70, 1.28–2.14). When we repeated the analysis using a multiple-level model (patients [level 1] nested within three different methods of cooling [level 2], which was nested within center [level 3]), the effect of hypothermia was comparable to the simpler random effects model (1.68, 1.29–2.08).

We assessed whether the effect of hypothermia interacted with age, gender, and duration from collapse to return of spontaneous circulation; none of these tests for interaction was significant. There was also no interaction between the effect of hypothermia and the method used to apply hypothermia ($\chi^2 = 2.92$, $df = 2$, $p = .23$).

Long-Term Effects of Hypothermia. One study followed patients up to 6 months or death, whichever occurred earlier. Being alive at 6 months with favorable functional neurologic recovery was more likely in the hypothermia group (risk ratio, 1.44; 95% confidence interval, 1.11–1.76). The intracluster correlation coefficient of this model was .02 (.002–.25, $p = .14$). This translates to a number-needed-to-be-treated of 6 (95% confidence interval, 4–25).

Controlling for the baseline variables age, gender, and time from collapse to return of spontaneous circulation slightly reduced the association between cooling and being alive at 6 months with favorable neurologic recovery (1.37, 1.02–1.72).

Safety of Hypothermia. One trial reported several predefined complications (41). Overall there was no difference in terms of "any complication." Any bleeding occurred more often in the hypothermia group (35 of 135 [26%] vs. 26 of 138 [19%]), but this was statistically not sig-

Table 1. Demographic data and cooling procedures

Trial	Age, Yrs	Female Gender No. (%)	VF No. (%)	ROSC, Mins	Target Temperature, °C	Time to Target Temperature, Mins	Maintenance of Hypothermia, Hrs After Start of Cooling	Method
HACA (41)	59 (51–68)	65 (24)	254 (92)	22 (16–30)	32–34	480 (240–960)	24	Cool air
Bernard (42)	68 (57–75)	25 (32)	77 (100)	24 (17–32)	33	150 (65–240)	12	Ice packs
Hachimi-Idrissi (49)	74 (66–79)	13 (39)	0	33 (27–37)	34	225 (90–240)	Up to 4	Helmet

VF, ventricular fibrillation; ROSC, return of spontaneous circulation; HACA, Hypothermia After Cardiac Arrest trial.
Continuous data are given as median and range from the 25th percentile to the 75th percentile.

Table 2. Long and short-term neurologic recovery

Trial	Hypothermia No. (%)	Normothermia No. (%)	Risk Ratio (95% CI)	*p* Value
Alive at hospital discharge with favorable neurologic recovery				
HACA (41)[a]	72/136 (53)	50/137 (36)	1.51 (1.14–1.89)[b]	.006[b]
Bernard (42)	21/43 (49)	9/34 (26)	1.75 (0.99–2.43)[b]	.052[b]
Hachimi-Idrissi (49)	3/16 (19)	0/17 (0)	7.41 (0.83–∞)[c]	.15[c]
Summary estimate			1.68 (1.29–2.07)	
Alive at 6 months with favorable neurologic recovery				
HACA (41)	71/136 (52)	50/137 (36)	1.44 (1.11–1.76)[b]	.009[b]

CI, confidence interval; HACA, Hypothermia After Cardiac Arrest trial.
[a]Two patients were transferred under sedoanalgesia to nonparticipating hospitals; neurologic outcome could not be assessed; it is known that these two patients survived until 6 months; [b] random effects models, center random; [c] Fisher's exact test and exact confidence limits (StatXact); the point estimate was calculated by adding 0.5 to each cell.

nificant ($p = .16$). There was a trend toward a higher incidence of sepsis in the hypothermia group (17 of 135 [13%] vs. nine of 138 [7%], $p = .09$). Other complications such as pneumonia, renal failure, or pancreatitis occurred equally often in both groups. One study (42) reported on "significant hemorrhagic complications," and there were none at all. In the study by Hachimi-Idrissi et al. (49), no significant complications possibly related to hypothermia occurred.

DISCUSSION

Key Findings. Inducing mild therapeutic hypothermia in patients who could be primarily successfully resuscitated from cardiac arrest improves neurologic survival in the short term. This beneficial effect appears to be independent of the method used to induce hypothermia. It appears that this also translates into improved favorable neurologic long-term survival up to 6 months after the event; this evidence is, however, based on a single trial only. The trials showed a benefit despite relatively slow cooling. Possibly, by faster cooling initiated immediately after arrival, the beneficial effects might have been even greater.

The trials were relatively heterogeneous in terms of clinical details. Two trials were multiple-center trials (41, 42); these two trials included only patients with ventricular fibrillation, except for a few patients whose electrocardiogram was reclassified after enrollment. Ventricular fibrillation is known to be associated with better outcome compared with other electrocardiogram rhythms. One trial only included patients with asystole and pulseless electrical activity (49), which are known to be associated with a grim prognosis (4, 5, 7, 9, 10, 14, 17). Three different methods were used to apply hypothermia. Active maintenance of hypothermia lasted 4 hrs, 12 hrs, and 24 hrs. The duration of applied hypothermia was protocol driven. Therefore, we cannot disentangle the impact of the duration of hypothermia from the type of hypothermia applied. Only comatose patients after cardiac arrest were included in the trials, as these patients were most likely to profit from a therapy that improves neurologic outcome. All these details may or may not contribute to heterogeneous outcomes but also increase the generalizability of our findings. It appears that the effect of hypothermia is largely independent of these factors and that the variability of the effect size was not influenced by type of hypothermia applied.

Several other limitations have to be mentioned. The meta-analysis was performed by the authors of the available three relevant trials. However, outcome assessors were blind to the intervention, which minimizes bias, and additionally individual patient data for the analysis could be used. Only CPC scores have been used to assess outcome. These are known to be only crude measures of neurologic recovery. Quality of life scores might have provided more differentiation of subjective perception of the patients (51) but were unfortunately not available. Unfortunately, only three rather small trials are currently available, but in a *post hoc* sensitivity analysis, we found that the results were relatively robust to a possible bias of allocation concealment.

By using individual patient data, we could assess whether hypothermia interacts with clinical variables. According to our analyses, the effect of the intervention does not interact with or depend on the age of the cardiac arrest victims or on the duration of the cardiac arrest. However, such interaction tests have a low power, and we might disregard a small effect even though present. All significance tests, however, exceeded a very conservative limit of .2.

Safety of Hypothermia. Even though we could not determine harmful effects of

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hypothermia, the data suggest the possibility of such harmful effects: increased risk of hemorrhagic complications and a higher rate of severe infections. In any case, the overall beneficial effect was not offset by the complications.

Clinical Implications. Even though the relative risk reduction appears to be moderate, the absolute risk reduction is certainly of clinical relevance as the baseline risk of unfavorable outcome is very high. Accordingly, we can be 95% confident that we may allow one additional patient to leave the hospital with favorable neurologic recovery by treating between 4 and 13 patients. This compares well with many pharmacologic interventions in patients with acute cardiovascular diseases.

In our experience, the application of mild therapeutic hypothermia is a simple intervention that does not necessarily require a substantial increase of resources. Exact temperature control is only possible with appropriate equipment (52), but perhaps an ice-cube maker and a refrigerator to store cold intravenous fluids (53) are also sufficient. However, inducing an exact temperature decrease and maintaining this temperature within narrow limits may be difficult by means of these simple techniques. Future modifications in cooling techniques should not be done uncritically, since this may influence the amplitude of the beneficial effect of hypothermia, either by ineffective cooling or by uncontrolled cooling causing unintended effects.

Research Implications. Future research programs need to assess several issues. It is of foremost importance to determine the effect of hypothermia on long-term prognosis and quality of life. Furthermore, the optimal duration for hypothermia needs to be determined. Finally, we need to know which method to cool patients is safe, cost-effective, and feasible on a large scale. A cluster-randomized trial would allow assessment of the effectiveness of hypothermia on an organizational level. Therefore, we report here the intracluster correlation coefficients to facilitate the planning of such trials.

CONCLUSION

Mild therapeutic hypothermia improves short-term neurologic recovery and survival in patients resuscitated from cardiac arrest of presumed cardiac origin. Its long-term effectiveness and feasibility at an organizational level need further research.

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