SELECTED ARTICLES

Should survivors of out-of-hospital cardiac arrest be treated with hypothermia?

Reviewed by: Colin Q.-T. Lee, MD; Joel Turner, MD; Eddy Lang, MD CM
McGill University, Sir Mortimer B. Davis–Jewish General Hospital, Department of Emergency Medicine, Montreal, Que.
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Clinical question

In patients who experience out-of-hospital VT/VF (ventricular tachycardia/fibrillation)-induced cardiac arrest and are resuscitated, does mild therapeutic hypothermia increase the likelihood of a favourable neurological outcome?

Article chosen

Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. The Hypothermia after Cardiac Arrest Study Group. *N Engl J Med* 2002;346(8):549-56.

Objective

To determine whether mild systemic hypothermia (i.e., target core temperature of 32°C–34°C over 24 hours) increases the rate of favourable neurologic outcome (i.e., the ability for independent living and working at least part-time) after resuscitation from cardiac arrest due to VT/VF.

Background

Out-of-hospital cardiac arrest is a major cause of death in developed countries. The estimated incidence in the United States is about 1/1000 population per year (15%–20% of all deaths). Survival rates are estimated to be from 5% to 35%. In patients who survive the initial resuscitation, residual neurologic damage has been estimated as between 10% and 70%. In order to decrease cerebral damage and the ischemia that occurs during and after initial resuscitation, the use of therapeutic hypothermia has been proposed. Human studies using moderate hypothermia in the late 1950s showed promise but had high complication rates. Using mild hypothermia, both animal studies and uncontrolled retrospective pilot studies with human subjects have demonstrated favourable neurologic outcomes. While the mechanism is not certain, it has been postulated that hypothermia decreases cerebral oxygen consumption and modifies other biochemical mechanisms, including calcium shifts, excitotoxicity, lipid peroxidation and other free-radical reactions, DNA damage and inflammation. Until now, no randomized controlled trials have shown mild hypothermia to be a feasible and effective treatment for cardiac arrest patients.

Population studied

Patients seen consecutively in the participating emergency departments (EDs) in whom spontaneous circulation (ROSC) had been restored after resuscitation from out-of-hospital cardiac arrest were recruited. Eligibility criteria are summarized in Box 1.

Study design

This randomized controlled trial ran at 9 sites in 5 European countries from 1996 to 2001. Block randomization with appropriate concealment was used, but care providers were not blinded to treatment assignment. All patients received standard intensive care as per a detailed protocol. Those assigned to the hypothermia group were cooled to a core temperature of 32°C–34°C using an external cooling mattress with a cover that delivered cold air over the entire body. The goal was to reach the target temperature (measured using a bladder temperature probe) within 4 hours after ROSC. Ice packs were applied if this goal was not achieved, and the target temperature was maintained for 24 hours after the onset of cooling. After the 24-hour cooling phase, patients were passively rewarmed to normothermia over an 8-hour period. Midazolam and fentanyl were used for sedation, and pancuronium (0.1 mg/kg every 2 hours for a total of 32 hours) was used to prevent shivering.

Outcomes measured

The primary outcome was a favourable neurologic outcome within 6 months of cardiac arrest, defined as a Glasgow–Pittsburgh Cerebral Performance Category 1 (good

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recovery) or 2 (moderate disability). Patients in these 2 categories were sufficiently functional to return to independent living and working at least part-time. Categories 3 (severe disability), 4 (vegetative state) and 5 (death) were considered adverse outcomes. Neurologic outcomes were assessed serially at predetermined time intervals, but only the 6-month neurological assessment was reported. The physicians responsible for neurologic assessments were blinded to treatment assignments. Secondary outcomes included overall 6-month mortality and 7-day complication rate. Complications included bleeding, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias and pressure sores. Analysis was based on intention-to-treat, and multivariate logistic regression was performed to determine strength of the treatment effect and to assess the importance of potential confounding variables.

Results

A total of 3551 patients were assessed for eligibility. Of these, 305 met inclusion criteria, but 30 were excluded for unspecified reasons. This left 137 patients in the hypothermia arm and 138 in the normothermia arm. The groups were similar at baseline, except that normothermia patients were more likely to have diabetes mellitus (19% vs. 8%) or coronary artery disease (CAD) (43% vs. 32%), and were more likely to have received bystander basic life support (49% vs. 43%). One patient in each group was lost to follow-up. Hypothermia was terminated early in 14 patients because of death ($n = 6$), arrhythmia and hemodynamic instability ($n = 3$), technical problems with the cooling device ($n = 2$), liver rupture ($n = 1$), previous participation in the trial ($n = 1$), and an error in cooling duration ($n = 1$). Table 1 shows that patients in the hypothermia group were more likely to have favourable neurologic outcomes (55% vs. 39%; absolute risk reduction [ARR] = 16%; number needed to treat [NNT] = 6). After controlling for potential confounding variables (diabetes mellitus, CAD, bystander basic life support), the relative risk (RR) improved slightly from 1.40 to 1.47 (95% confidence interval [CI], 1.09–1.82).

For the secondary outcome of mortality at 6 months, 56/137 patients (41%) died in the hypothermic arm, compared to 76/138 patients (55%) in the normothermia arm, for an NNT of 7 (Table 1). After adjustment for baseline variables, the RR strengthened from 0.74 to 0.62 (95% CI, 0.36–0.95). There were no statistically significant differences in the other secondary outcomes, although there was a trend toward increased infections in the hypothermia group.

Box 1. Study criteria

Inclusion criteria

Witnessed cardiac arrest with presumed cardiac cause
Initial rhythm of ventricular fibrillation or nonperfusing ventricular tachycardia
Age between 18 and 75 years
Estimated time from collapse to initial resuscitation of 5 to 15 minutes
No more than 60 minutes from collapse to ROSC

Exclusion criteria

Cardiac arrest occurring after the arrival of EMS personnel
Initial temperature below 30°C
Pre-arrest coma due to central nervous system depressant drugs
Hypotention (MAP <60 mm Hg) for more than 30 minutes after ROSC
Hypoxemia (oxygen saturation less than 85%) for more than 15 minutes after ROSC
Response to verbal commands after ROSC
Factors making successful follow-up unlikely
Pre-existing terminal illness, coagulopathy, pregnancy or enrollment in another study

ROSC = return of spontaneous circulation; MAP = mean arterial pressure; EMS = emergency medical services

Table 1. Neurologic outcome and mortality at 6 months

	Group				
Outcome	Normothermia	Hypothermia	Risk ratio (95% CI)	*p*	NNT (95% CI)
Favourable	54/137 (39%)	75/136 (55%)	1.40 (1.08–1.81)	0.009	6 (4–25)
Death	76/138 (55%)	56/137 (41%)	0.74 (0.58–0.95)	0.02	7 (4–33)

CI = confidence interval; NNT = number needed to treat

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Study conclusions

In the patients who had ROSC following resuscitation, but failed to regain consciousness before randomization, mild therapeutic hypothermia not only reduced mortality but also significantly increased the rate of meaningful neurologic survival.

Commentary

There is a high incidence of delayed mortality and neurologic impairment after successful resuscitation from an out-of-hospital cardiac arrest.[1] As well, the financial costs associated with permanent neurologic impairment for the patient and the health care system are high. This European study and an Australian study,[2] both published in the same issue of the *New England Journal of Medicine,* are the first randomized controlled studies to show that the use of mild hypothermia (32°C–34°C) post-ROSC improves neurologic outcomes and decreases mortality without increasing the number of severely disabled survivors. The European study methodology was strong, and results showed that in order to prevent one unfavourable neurologic outcome and one death at 6 months, only 6 and 7 patients respectively needed to be treated.

The Australian study[2] employed alternate-day randomization to enroll 77 patients who remained comatose after ROSC, to receive normothermic treatment or hypothermia initiated by emergency medical services in the field using ice packs. Unlike the European study appraised here, hypothermia was only maintained for 12 hours prior to gradual rewarming; however, results were much the same, with 49% discharged home or to a rehabilitation facility, compared to only 26% in the normothermia group ($p = 0.046$). The NNT for a favourable neurologic outcome was 4. There was also a trend ($p = 0.145$) toward improved mortality (51% vs. 68%).

Despite the randomization process, however, more patients in the normothermia group of both studies received bystander CPR (a prognostic factor associated with improved survival[3]) than in the hypothermia group. This discrepancy should actually strengthen the conclusions of the study. In the European study the normothermia group had more patients with diabetes (19% vs. 8%) and more with CAD (43% vs. 32%) than did the hypothermia group. Although there is no evidence that existence of these conditions predicts a poor outcome in cardiac arrest survivors, these 2 characteristics are risk factors for cardiac arrest.[4] Using multivariate logistic regression to adjust for these baseline differences between study groups, the beneficial effect of hypothermia remained undiminished. Despite scrupulous randomization, additional undocumented risk factors may have increased the heterogeneity between the 2 groups, impacting the outcome.

Although blinding during the active treatment phase was impossible, both studies employed a standardized ICU protocol for hemodynamic, ventilatory and shivering control for both groups to limit the potential for bias. There were no statistically significant differences in measured adverse effects, suggesting a relatively safe intervention. It should be noted, however, that 50% of the hypothermia group developed pneumonia or sepsis versus 36% for the normothermia group. Bleeding events were also higher (26% vs. 19%) in the hypothermia group. This may be important, since moderate hypothermia (28°C–32°C) is reportedly associated with increased rates of arrhythmias, ventricular fibrillation, coagulopathy and infection.[5,6]

Follow-up in the European study was outstanding, with the loss of a single patient from each group. While both studies used blinded outcome assessors, the European study employed a previously validated tool, the Pittsburgh cerebral-performance scale, and followed the patients up to 6 months.

Given the notoriously poor prognosis for out-of-hospital cardiac arrest patients, any intervention that improves outcomes without increasing the numbers of severely disabled or vegetative patients is most welcome. In addition, the therapy is easy to apply, non-invasive and not overtly expensive. Compared to other cardiac arrest interventions that have been attempted to improve the rates of survival to discharge (i.e., high dose epinephrine, amiodarone[7,8]), the results of the European hypothermia study are clearly superior. The only note of caution may be that, despite their results, both sets of authors recommended further study. Also a review of the animal studies leading up to the human trials indicated that hypothermia was instituted immediately following ROSC and that delaying the initiation of mild hypothermia for even 15 minutes negated the beneficial effects,[8] something that may be difficult to prevent in clinical practice.

Competing interests: None declared.

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Correspondence to: Dr. Colin Q.-T. Lee, University of Toronto, Department of Public Health Sciences, Community Medicine Residence Program, 4th floor, McMurrich Building, 12 Queen's Park Cr., Toronto ON M5S 1A8; cqt.lee@utoronto.ca

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