Pro - con debate

Therapeutic Hypothermia After Cardiac Arrest - Not so Fast

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ABSTRACT

The concept of hypothermia as a protective strategy for various kinds of brain injury is far from new. Multiple mechanisms have been implicated including reduction in neuronal apoptosis, inhibition of excitatory processes caused by ischaemia and reperfusion, alterations in intracellular cation concentrations due to ion pump dysfunction, suppression of inflammatory cytokines, reduction of free radical production and reduction of cerebral oedema. Despite support from animal studies, convincing clinical evidence was lacking until recently. Two high quality clinical trials now support the use of hypothermia following cardiac arrest, but a number of issues remain. The main limitation of both trials is their highly selective entry and exclusion criteria, which limit their applicability to the majority of cardiac arrest patients. Questions about the initiation, duration, rewarming rate and the technique for producing hypothermia remain unanswered. There is also concern that side effects of hypothermia have the potential to counteract any potential benefit. (**Critical Care and Resuscitation 2005; 7: 322-324**)

Key words: Cardiac arrest, therapeutic hypothermia, review

Background and rationale[1]

The idea that hypothermia could be therapeutic dates back to ancient times. It was used by the ancient Egyptians, Greeks and Romans, and Hippocrates advocated its use for the reduction of haemorrhage. The protective value of accidental hypothermia in drowning has been described since the 1930s, and the first case series of therapeutic hypothermia for head injury was published in 1945.[2] This and subsequent studies used relatively deep hypothermia (< 30°C), which resulted in unacceptable side effects and management difficulties. However, animal experiments in the 1980s suggested that similar benefits could be obtained with milder (32 - 35°C) hypothermia without these problems.

Traditionally, the benefits of hypothermia were thought to be due to slowing of cerebral metabolism;[3] however, other mechanisms are probably more important. These include a reduction in neuronal apoptosis,[4] inhibition of excitatory processes caused by ischaemia and reperfusion,[5] alterations in intracellular cation concentrations due to ion pump dysfunction,[5] suppression of inflammatory cytokines,[6] reduction of free radical production[7] and reduction of cerebral oedema.[8]

Hypothermia has been applied clinically to head injury, stroke, subarachnoid haemorrhage, neurosurgery, cardiac and vascular surgery, but most interest has focused recently on its use following resuscitation from cardiac arrest. Although a number of small and low-quality trials in the 1980s and 1990s suggested moderate hypothermia might be of benefit following cardiac arrest, two randomised controlled trials,[9,10] both published in 2002, have resulted in its widespread acceptance and enthusiastic adoption.[11]

The Australian study

In a study carried out in Melbourne, Australia by

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Bernard *et al*,[9] 77 patients were assigned following successful resuscitation, according to the day of the month, to active cooling to achieve a core temperature of 33°C within two hours, or normothermia. Cooling was achieved by the use of ice packs to the head and torso, and was maintained for 12 hours. Active warming was instituted after 18 hours. The primary endpoint was hospital discharge with a neurological outcome sufficient for discharge home or to a rehabilitation facility, as assessed by a blinded rehabilitation physician. Although there was no significant difference in mortality between the two groups, there was a significant difference in the rate of good neurological outcome, as defined above; 21 of 43 patients (49%) in the hypothermia group vs. 9 of 34 patients (26%) in the normothermia group.

It is important to note that the inclusion criteria for this study were strict, resulting in a 33-month recruiting period despite the relatively small number of patients. Only patients with ventricular fibrillation at the time of paramedic arrival, return of spontaneous circulation without shock, age over 18 for men and over 50 for women, were included. Patients for whom an alternative cause of coma was considered possible, including drug overdose, head trauma or stroke, were excluded.

Moreover, of 84 patients initially eligible, 7 were excluded for logistic or consent reasons, 4 patients assigned to the hypothermia group did not receive it, and one patient assigned to normothermia became spontaneously hypothermic. There were also significant differences in gender and the frequency of bystander CPR between groups. All these factors have the potential to confound the results. It is also of interest to note that all patients were treated with intravenous lignocaine (bolus plus 24 hour infusion), and pulmonary artery catheters were used in almost all patients.

The European study

The study by Holzer *et al*,[10] almost 4 times larger than the Melbourne trial, had even stricter entry criteria. These comprised ventricular fibrillation or pulseless ventricular tachycardia, witnessed arrest, presumed cardiac aetiology, age range 18 – 75, a "down-time" of no more than 15 minutes and ROSC no longer than 1 hour from collapse. Exclusions were also stricter than the Melbourne study, including hypotension, hypoxemia and "factors that made participation in follow-up unlikely". In fact, 92% of those screened were deemed ineligible for this trial. This is an important statistic in assessing the generalisability of the results, and it is a pity that corresponding data were not provided by Bernard's group.

The primary outcome variable was more rigorously defined than in Melbourne, and follow-up was continued for 6 months. Cooling was done by means of a proprietary cold air inflated mattress and cover, and the aim was to achieve target temperature within 4 hours, rather than commencing in the pre-hospital phase as prescribed by Bernard's group. However, cooling was maintained for 24 hours, with only passive rewarming thereafter. Neither pulmonary artery catheters nor antiarrhythmic drugs were mandated in this study. Matching was better than in the Melbourne study, though the normothermia group had a higher rate of diabetes (more than double) and known coronary artery disease, both of which were potentially significant confounders.

In practice, it took a median of 8 hours to achieve the target temperature in the hypothermia group, and in 19 of 132 patients (14%) the target could not be reached. Nevertheless, 75 of 136 patients (55%) in the hypothermia group had a favourable neurological outcome, compared with 39% in the normothermia group, a statistically significant result. In contrast to Bernard *et al*, this trial showed a significant benefit for mortality with hypothermia – 41% vs. 55%

Issues and applicability to clinical practice

The Bernard study, though a well designed randomised controlled trial, is small, the groups are not especially well matched and there is some crossover (10%) between treatment assignments. It supports the use of hypothermia only in males over 18 and women over 50 in whom ventricular fibrillation is the presenting rhythm and the underlying aetiology includes no other potential causes of coma. It assumes the institution of hypothermia pre-hospital and its maintenance for less than 24 hours.

The European trial, though larger and equally rigorous, also has some matching issues and extremely restricted eligibility criteria. Hypothermia was attained by what appears to be a much slower and less effective technique, but the general care of patients was perhaps more conventional than in Melbourne (no pulmonary artery catheters or lignocaine). Overall outcomes were better, presumably on the basis of entry criteria, but a similar benefit for neurological outcome was demonstrated when hypothermia was used.

To put these studies in perspective, it is useful to review the overall outcome of out-of-hospital cardiac arrests in Melbourne in 2002,[12] the same year both trials were published. Of 1331 cardiac arrest calls to the ambulance service, 778 were pronounced dead on arrival of the ambulance team. Of the 553 in whom CPR was started, 105 reached hospital alive, of whom 40 survived to hospital discharge, i.e. 3% of cardiac arrest calls or 7% of those in whom CPR was commenced. 155 patients – 11% of calls or 28% of

those in whom CPR was commenced – were initially assessed as ventricular fibrillation of presumed cardiac cause. Only 26 of these patients – 2% of arrest calls or 5% of those in whom CPR was commenced – survived to hospital discharge.

Even accepting their technical shortcomings, in the current Australian context of out-of-hospital arrest, the two pivotal hypothermia trials are properly applicable to about a quarter of cases where CPR is commenced, and could be expected to improve the outcome of only 5% of these. Questions about the initiation, duration, rewarming rate and the technique for producing hypothermia – all tackled quite differently in the two trials – remain completely open.

In addition, the potential adverse effects of hypothermia need to be carefully considered. These include abnormalities of glucose and fat metabolism, cardiovascular, electrolyte, immunological and haematological problems, and altered drug pharmacokinetics[13] If the promise of therapeutic hypothermia is to be translated into real clinical benefit, the highest standard of general intensive care will be required.

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