

# PRACTICE

## UNCERTAINTIES PAGE

# Should children who have a cardiac arrest be treated with therapeutic hypothermia?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic, please email us at [practice@bmj.com](mailto:practice@bmj.com).

The International Liaison Committee for Resuscitation recommends that comatose adult patients with spontaneous circulation after cardiac arrest are cooled to 32-34°C for 12-24 hours based on analysis of data from two randomised controlled trials and 17 observational studies.<sup>1</sup> However, these studies were mostly in a specific subgroup of cardiac arrest patients with witnessed, out-of-hospital ventricular fibrillation, and evidence of benefit in the general population of cardiac arrest patients has been less certain.<sup>2</sup> The rationale for therapeutic hypothermia is that it can reduce cerebral metabolism, attenuate biosynthesis of excitotoxic compounds, reduce free radical production, reduce inflammation, and regulate gene and protein expressions associated with necrotic and apoptotic pathways during ischaemia and reperfusion.<sup>3</sup>

Recommendations for treatment in children<sup>4</sup> (box 1) are based almost solely on adult data. However, the aetiology of cardiac arrest is very different in children,<sup>5</sup> possibly altering the pattern of neuronal injury. Most cardiac arrests are secondary to a respiratory cause with profound hypoxia, and primary cardiac causes of arrests, including ventricular fibrillation, are rare. In other clinical situations, therapeutic hypothermia has been seen to be both beneficial (newborns with hypoxic brain injury within 6 hours of birth)<sup>6</sup> and potentially harmful (traumatic brain injury).<sup>7</sup> It is therefore important that the question of whether children with cardiac arrest should be treated with therapeutic hypothermia is addressed.

## What is the evidence of uncertainty?

Our recent Cochrane systematic review<sup>8</sup> searched, to December 2011, the Cochrane Anaesthesia Review Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, BIOSIS, and Web of Science databases for randomised controlled trials comparing therapeutic hypothermia with normothermia or standard care after paediatric cardiac arrest. We also contacted international experts in therapeutic hypothermia and paediatric critical care to locate further published and unpublished studies.

We found no relevant randomised controlled trials, but identified three paediatric cohort studies: two retrospective studies<sup>9,10</sup> and one prospective study in abstract form only.<sup>11</sup> All three studies showed no difference in mortality or proportion of survivors with good neurological outcome for those treated with therapeutic hypothermia compared with standard care. Imbalance between the compared populations within studies was evident, as was heterogeneity in the cause of cardiac arrest. Patients receiving therapeutic hypothermia were sicker with longer duration of cardiopulmonary arrest, more pharmacological interventions during resuscitation, higher post-resuscitation serum lactate levels, higher multiorgan dysfunction score, and requirement for renal replacement therapy.

Prospective observational studies of children undergoing therapeutic hypothermia provide evidence that the treatment is safe and feasible, but not of its effectiveness.<sup>12,13</sup> Use of therapeutic hypothermia has also been reported in retrospective observational studies, but the incidence was too low to report effectiveness.<sup>14-16</sup>

Surveys of clinical practice in the United Kingdom and the United States show that therapeutic hypothermia is used by some paediatric intensive care and emergency medicine units

**Box 1: Recommendations for use of therapeutic hypothermia after paediatric cardiac arrest (International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations<sup>4</sup>)**

- Therapeutic hypothermia (32–34 °C) **may be beneficial** for adolescents who remain comatose after resuscitation from sudden, witnessed, out-of-hospital, ventricular fibrillation cardiac arrest
- Therapeutic hypothermia (32–34 °C) **may be considered** for infants and children who remain comatose after resuscitation from cardiac arrest

after both out-of-hospital and in-hospital cardiac arrest, but there was substantial variation in practice regarding patient selection, temperature, and duration of therapy.<sup>17 18</sup>

## Is ongoing research likely to provide relevant evidence?

Our recommendations for the framing of future research to answer this clinical uncertainty are outlined in box 2. Our search of the trials registry databases (detailed above) identified four ongoing randomised controlled trials.

The two Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trials (350 and 500 participants) will determine whether, among children aged <18 years with in-hospital cardiac arrest (NCT00880087) or out-of-hospital cardiac arrest (NCT00878644), treatment with a protocol involving hypothermia (32–34°C) for 48 hours and three days of normothermia (36–37.5°C), compared with five days of normothermia, affects neurological outcome at 12 months.

The Hypothermia for Cardiac Arrest in Paediatrics (NCT00754481) phase II (pilot) trial (n=40) will determine if children aged <18 years with in-hospital or out-of-hospital cardiac arrest treated with 48 hours of hypothermia (33–34°C) compared with normothermia (36.5–37.5°C) have different neurological outcomes at 12 months.

The use of a strict normothermia group in these three trials aims to eliminate a confounding effect of hyperthermia in the control group, as was noted in about 25% of the European trials of hypothermia after cardiac arrest in adults.<sup>19</sup> Hyperthermia ( $\geq 38^\circ\text{C}$ ) is harmful and associated with unfavourable neurological outcome after hypoxic brain injury.<sup>20</sup>

The fourth ongoing study is the Duration of Hypothermia for Neuroprotection After Pediatric Cardiac Arrest (NCT00797680) phase II (pilot) trial (n=40) determining if children aged <18 years after in-hospital or out-of-hospital cardiac arrest treated with 72 hours of hypothermia (32–34°C) compared with 24 hours of hypothermia (32–34°C) develop less brain injury (assessed by plasma biomarkers and magnetic resonance spectroscopy).

Clinical trials in paediatric critical care are challenging because of the low incidence of critical illness in children. As a result, paediatric trials often adopt wide inclusion criteria. The heterogeneity of patients, particularly among those with out-of-hospital cardiac arrest, may result in mixed inclusion of hypoxia induced cardiac arrests (such as asthma) and cardiac causes (such as primary arrhythmias), potentially masking a treatment effect in a particular subgroup. The current studies will not provide definitive evidence for the optimal duration of therapeutic hypothermia (24, 48, 72 hours, or longer), rewarming rates after hypothermia, timing of the start of treatment, or method of temperature manipulation. As two of the four trials are small pilot studies, these also will not be able to provide evidence of effectiveness.

## What should we do in the light of the uncertainty?

Managing a comatose child or infant after return of spontaneous circulation after cardiac arrest is a rare event outside specialist centres. Early consultation with a paediatric intensive care specialist is strongly recommended in all cases. In the absence of definitive evidence it is reasonable to initiate therapeutic hypothermia for comatose adolescent survivors from a ventricular fibrillation or pulseless ventricular tachycardia cardiopulmonary arrest, based on the evidence from adult clinical trials (box 1).<sup>4</sup> Therapeutic hypothermia may also be considered for infants and children who remain comatose after resuscitation from cardiac arrest. In all cases avoid hyperthermia ( $\geq 38^\circ\text{C}$ ) and when possible consider enrolment in ongoing randomised controlled trials or registration in existing national databases such as the Paediatric Intensive Care Audit Network ([www.picanet.org.uk](http://www.picanet.org.uk)) and UK National Cardiac Arrest Audit ([www.icnarc.org](http://www.icnarc.org)).

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**Box 2: Recommendations for future research**

The key components of the research required to reduce our clinical uncertainty in the use of therapeutic hypothermia after paediatric cardiac arrest

*Population*

- Infants and children experiencing an in-hospital or out-of-hospital cardiac arrest at risk of neurological injury.
- Inclusion of sufficient patients to allow subgroup analysis of the impact on outcome of:
  - Cause of cardiac arrest—*asphyxia induced or of cardiac origin*
  - Presenting cardiac rhythm at time of cardiac arrest—*shockable (ventricular fibrillation or ventricular tachycardia) or non-shockable (asystole and pulseless electrical activity).*

*Intervention*

- Therapeutic hypothermia administered within a defined dose:
  - Time to initiation of therapeutic hypothermia
  - Time to reach target temperature
  - Specify method used for cooling
  - Duration of at least 24 hours, up to 72 hours
  - Temperature depth in the range 32-34°C
  - Controlled rewarming rate no faster than 0.25°C per hour.

*Comparison*

- Strict normothermia (36-37°C), actively avoiding hyperthermia ( $\geq 38^\circ\text{C}$ ).

*Outcome*

- Long term survival, neurocognition, and developmental ability.
- Safety of intervention (rate of infections, bleeding, arrhythmias, metabolic derangement).
- Potentially using early biomarkers if validated with longer term clinical outcomes.

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