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Does the evidence support the use of mild hypothermia after cardiac arrest? No

Several guidelines recommend hypothermia for comatose patients who have had a cardiac arrest outside hospital. **Jerry Nolan** and **Jasmeet Soar** (doi:10.1136/bmj.d5830) believe the data support this advice, but **Andrew Walden**, **Niklas Nielsen**, and **Matt Wise** question the quality of the evidence

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Historically, critical care physicians had a nihilistic approach towards patients who remained unconscious after a cardiac arrest outside hospital. This changed with the publication of two randomised clinical trials of mild induced hypothermia (32-34°C) that showed neuroprotection.[1 2] Subsequently this treatment has been embraced by the International Liaison Committee on Resuscitation, European Resuscitation Council, American Heart Association, and, most recently, the National Institute for Health and Clinical Excellence (NICE).

Animal models of cardiac arrest showed that mild hypothermia improved neurological outcome,[3] and these data were supported by small observational studies in patients. Clinical trials to determine whether this treatment benefited unconscious patients after cardiac arrest were therefore fitting. However, neither the above randomised trials[1 2] nor subsequent studies[4] provide sufficiently robust data to justify the conclusion that cooling to 32-34°C should be used after cardiac arrest outside hospital.

Evidence from clinical trials

A search for the terms "cardiac arrest" and "hypothermia" in PubMed identifies over 1800 publications since 2002, but they are almost all reviews, expert opinion, registries, and observational studies. Systematic review and meta-analysis, including a Cochrane review by Arrich and colleagues[5] concluded that mild hypothermia should be used after out of hospital cardiac arrest. Arrich and colleagues identified five published randomised trials, including one in abstract form,[1 2 4 6 7] and concluded that mild hypothermia was beneficial. However, the review did not rigorously evaluate the risks of random error, design flaws, and high risk of bias in these trials and failed to use the GRADE system[8] to assess evidence quality. This may have resulted in an overestimation of the treatment effect.

The largest clinical trial to date, undertaken by the Hypothermia After Cardiac Arrest Group,[1] recruited an average of just over one patient a week from nine centres over five years. Only 275 patients were randomised from 3551 screened, and this low inclusion rate of around 8% makes it difficult to generalise results to daily clinical practice. The study was discontinued because of slow recruitment and a lack of funding rather than because of defined stopping rules, and, importantly, there was no predefined power calculation. The level of coma before randomisation was not reported, and withdrawal of critical care was not standardised, introducing potential bias to the primary outcome measures of neurological outcome and death.[9]

The four other randomised clinical trials included in the Cochrane review also had methodological problems. Examples include quasirandomisation with odd and even dates,[2] early stopping without predefined rules,[4] unplanned adaptive design,[2] baseline differences between groups,[2 4 6 7] selective outcome reporting, and no description of sequence generation and allocation concealment[6 7] or blinding.[4 6 7] Reporting of adverse outcomes is also inconsistent, making it difficult to assess the harm from this treatment. Recognised adverse effects include increased risk of infection, haemodynamic instability, arrhythmias, coagulopathy, hyperglycaemia, and electrolyte abnormalities.[10 11] In one prospective observational registry based study of 765 patients treated with hypothermia after cardiac arrest outside hospital adverse events were common and included pneumonia (48%), electrolyte imbalance (37%), seizures (24%), arrhythmias (14%), bleeding (6%), and sepsis (4%).[11]

Recently Nielsen and colleagues[12] conducted a systematic review and meta-analysis of hypothermia after cardiac arrest and identified 478 patients from the same five trials[1 2 4 6 7] included in the Cochrane review.[5] They systematically evaluated the benefits and harms of the intervention, taking into account risk of systematic bias and random errors. Treatment effects were quantified using meta-analyses and trial sequential analysis,

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which reduces the risk of type I errors in cumulative meta-analysis.[13] The authors concluded that there was a lack of firm evidence of a beneficial effect of mild hypothermia and that using the GRADE system the quality of evidence was low. The recent NICE guideline did not consider this systematic review, even though it was published before the evidence synthesis was conducted.

The future

Experimental data show that mild hypothermia may be neuroprotective after cardiac arrest.[3] However, the risks and benefits of hypothermia in an animal that is healthy before an experimental cardiac arrest are not the same as those in patients with vascular disease and multiple comorbidities. Adverse events relating to hypothermia have been poorly studied in people who have had a cardiac arrest and need to be examined in future clinical trials. An international, multicentre randomised controlled trial of temperature management in unconscious survivors of out of hospital cardiac arrest (randomised to 33°C or 36°C) is underway. The study overcomes many of the methodological problems of previous trials, including standardised withdrawal, blinded assessment, rigorous evaluation of adverse events, defined stopping rules, and powered for a primary outcome measure of survival.[14]

Data from current clinical trials are not sufficiently robust to justify the conclusion that mild hypothermia should be used routinely in unconscious survivors of out of hospital cardiac arrest. We need data from adequately designed and powered studies. Until these are available, the recommendations must be regarded as weak and should not be allowed to inhibit further research into the effects of temperature control.

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Several guidelines recommend hypothermia for comatose patients who have had a cardiac arrest outside hospital. **Jerry Nolan** and **Jasmeet Soar** believe the data support this advice, but **Andrew Walden**, **Niklas Nielsen,** and **Matt Wise** (doi:10.1136/bmj.d5889) question the quality of the evidence

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The use of mild hypothermia in comatose survivors of cardiac arrest has been shown to improve neurological outcome in both animals and humans.[1 2] The evidence of benefit is strongest for people who have had a ventricular fibrillation cardiac arrest outside hospital, but data are beginning to emerge supporting its use in other types of arrest.

Supportive evidence

A randomised trial[3] and a pseudorandomised (by day of the month) trial[4] of cooling unconscious patients to 32-34ºC after ventricular fibrillation cardiac arrest outside hospital both recorded benefits.[3 4] The randomised Hypothermia After Cardiac Arrest (HACA) study enrolled 275 patients (8% of those assessed).[3] Those in the hypothermia group were sedated, paralysed, ventilated, and surface cooled to 32-34°C for 24 hours. Seventy five (55%) of the 136 in the hypothermia group showed a favourable neurological outcome at 6 months compared with 54 (39%) of 137 in the normothermia group (risk ratio=1.4, 95% confidence interval 1.08 to 1.81; number needed to treat (NNT)=6). Mortality at 6 months was 41% (56/137) in the hypothermia group and 55% (76/138) in the normothermia group (risk ratio=0.74, 0.58 to 0.95; NNT=7). In the smaller pseudorandomised Australian trial, there was good neurological outcome at hospital discharge in 49% (21/43) of the hypothermia group compared with 26% (9/34) of the normothermia group (unadjusted odds ratio 2.7, 95% confidence interval 1.02 to 6.88; NNT=4.5), although mortality was not significantly different (51% *v* 68%).[4]

On the basis of these controlled trials, animal data,[1] and other supportive clinical data,[5] the International Liaison Committee on Resuscitation recommended in 2003 that unconscious adults who have been resuscitated after ventricular fibrillation cardiac arrest outside hospital should be cooled to 32-34°C for 12-24 hours.[6] The committee added that although mild hypothermia may be beneficial for other cardiac arrest rhythms or after in-hospital cardiac arrest, data were insufficient to enable a firm recommendation. This statement was designed to encourage further research.

Since the publication of the committee's advisory statement, several lower quality studies with historical control groups have shown improvement in neurological outcome or survival with mild hypothermia after cardiac arrest outside hospital.[2] Two non-randomised studies with concurrent controls suggested benefit in patients with cardiac arrest from other rhythms in or out of hospital.[7 8] However, the quality of the data was not sufficient for the committee to change its advice in the updated 2010 recommendations.[9]

Recently, information from an internet based survey and a Dutch national intensive care database showed that mild hypothermia was associated with a 20% relative reduction (95% confidence interval 0.65 to 0.98) in hospital mortality among 5317 patients (1547 treated before hypothermia was introduced and 3770 after implementation) admitted to intensive care after cardiac arrest (all rhythms and occurring both in and out of hospital).[10]

Uncertainty

Questions remain about the best way to use hypothermia after cardiac arrest. Most of the studies have cooled patients to 32-34°C, but the optimal temperature is unknown. The optimal cooling method, onset, duration, and rewarming rate, and therapeutic window are also unknown. Furthermore, the HACA and Australian studies were by no means perfect. It was impossible to blind the cooling treatment, so the clinicians who later made decisions on withdrawal of treatment were likely to have been aware which patients had received mild hypothermia. In both studies, the temperature of the patients in the control arms was not controlled and some of these patients were pyrexial (>37.5°C), a factor associated with worse neurological outcome.[11] These problems led to a recent report from five

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professional societies rating the evidence as only moderate, although it still recommended targeted temperature management for ventricular fibrillation cardiac arrest outside hospital.[11] No recommendation was made for cooling after cardiac arrest in other circumstances.

In our view, the evidence is good enough to support the use of mild hypothermia after out of hospital ventricular fibrillation cardiac arrest. The neurological outcome after cardiac arrest in other circumstances is generally worse, and the evidence for using mild hypothermia in these cases is much weaker. But harm from mild hypothermia is confined mainly to increased infection,[12] and the severity of the ischaemia-reperfusion insult is probably more important than arrest location and rhythm. This may partly explain why many clinicians also cool comatose patients after cardiac arrest from other rhythms and in-hospital arrest.[13]

Finally, observational studies show that mild hypothermia after cardiac arrest as part of a package of care that includes interventions such as percutaneous coronary intervention and glucose control improves long term outcomes.[14 15] Although there are unanswered questions about the optimal delivery of a targeted temperature strategy, the good news for comatose cardiac arrest patients is that the use of mild hypothermia seems to improve both survival and subsequent quality of life.

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