

# Critical Review Form

## Meta-analysis

Hypothermia for neuroprotection after cardiac arrest: Systematic review and individual patient data meta-analysis, *Crit Care Med* 2005;33:414-418

**Objectives:** To access the therapeutic effect of induced hypothermia in survivors of primary cardiac arrest via a systematic review of the literature and individual patient data meta-analysis (p.414)

**Methods:** The Systematic Review authors (all investigators in previous international controlled trials being analyzed by PGY III and IV today) searched MEDLINE, EMBASE, CINAHL, PASCAL, BIOSIS, and Cochrane from 1990 – November 2002 for randomized and quasi-randomized controlled trials of therapeutic hypothermia ( $< 35^{\circ}\text{C}$ ) within 6-hours of ED arrival to adult survivors of cardiac arrest. They also scanned the references of relevant studies and reviews. They used the following definitions:

**Favorable short-term outcome** – good neurological recovery and discharge from the hospital.

**Favorable long-term outcome** – good neurological recovery and being alive 6-months after the cardiac arrest.

**Good neurological recovery** – conscious, alert, sufficient cerebral function for activities of daily life with or without hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes (cerebral performance category 1 or 2).

Individual trial quality was assessed qualitatively by assessing allocation sequence generation, allocation concealment and blinded outcome assessment. Individual patient data was supplied by trial principal investigators and meta-analysis was performed by intention to treat principle using random-effects logistic regression and generalized linear modeling.

<b>Guide</b>	<b>Question</b>	<b>Comments</b>
<b>I</b>	<b><i>Are the results valid?</i></b>	
1.	Did the review explicitly address a sensible question?	Yes – does therapeutic hypothermia improve patient important cerebral performing after cardiac arrest related coma?
2.	Was the search for relevant studies details and exhaustive?	Yes – multiple search engines used and a secondary bibliography review was performed. Although this meta-analysis was published in 2005, the search spanned only 1990-2002 – the authors could have extended the search until immediately prior to submission
3.	Were the primary studies of high methodological quality?	Unknown since the authors neglect to use a validated quality review tool like Jadad's
4.	Were the assessments of the included studies reproducible?	Unknown since a validated assessment tool was not used and SR author grading of studies was not reported quantitatively.
<b>II.</b>	<b><i>What are the results?</i></b>	

1.	What are the overall results of the study?	<ul style="list-style-type: none"> <li>• Among the 991 hits, seven controlled trials were identified but three used historical controls and one assessed whether hypothermia application while performing ACLS was feasible. Thus, three trials were included in this meta-analysis: <ul style="list-style-type: none"> <li><u>HACA</u> (PGY IV paper) – large European study of 275 patients with random sequence allocation and blinded outcome assessors.</li> <li><u>Bernard</u> (PGY III paper) – Australian trial of 77 patients with odd/even day allocation and blinded outcome assessors.</li> <li><u>Hachimi-Idrissi</u> – European single-center subset of HACA involving only PEA/asystole survivors and using a head/neck helmet device rather than the HACA cooling blanket. Random number generator was used and outcome assessors were blinded. This trial enrolled 33 subjects.</li> </ul> </li> <li>• <b><u>Short-Term Effects:</u></b> hypothermia treated patients were more likely to be discharged with no or minimal neurological damage (risk ratio, 1.68; 95% CI, 1.29-2.07) with <b>NNT = 6</b> (95% CI 4 – 13).</li> <li>• When analysis of outcomes was repeated for CPC 1 (no neurological deficits) the effect remained unchanged (RR 1.64, 1.25-2.05)</li> <li>• Controlling for baseline variables (age, gender, time to ROSC) did not reduce the effect nor did a nested analysis by patient, method of cooling, or center. In fact, <u>the method of attaining hypothermia did not impact outcomes in any way.</u></li> <li>• <b><u>Long-Term Effects</u></b> – being alive at 6-months with favorable neurological recovery was more likely in the hypothermia group (RR 1.44, 1.11-1.76) with <b>NNT = 6</b> (95% CI 4-25), an effect unchanged when controlling variables.</li> </ul>
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		<ul style="list-style-type: none"> <li>• Safety analysis revealed a non-significant trend towards increased bleeding (26% vs. 19%, p = 0.09) and sepsis (13% vs. 7%, p=0.09) in the hypothermia treated groups.</li> </ul>
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2.	How precise are the results?	The upper limits of NNT CI would not dissuade my use of this therapy. Therefore, the effects are sufficiently precise.
3.	Were the results similar from study to study?	No, the three studies were significantly different in terms of rhythm (VF vs. PEA/asystole), method of cooling (ice vs. cooling blanket vs. helmet), speed of cooling, and duration of hypothermia. The SR made no attempt to perform statistical tests of heterogeneity (I <sup>2</sup> or Q-test), but their individual patient data meta-analysis model seemed robust when analyzed by method of cooling, so heterogeneity may be insignificant.
<b>III.</b>	<b><i>Will the results help me in caring for my patients?</i></b>	
1.	How can I best interpret the results to apply them to the care of my patients?	Therapeutic hypothermia for post VF (and perhaps post PEA/asystole) cardiac arrest by cooling blanket, helmet or ice improves neurologically intact, outcomes both short- and long-term with no significant adverse effects.
2.	Were all patient important outcomes considered?	No. Patient quality of life scores would be superior to CPC scores which are surrogate numbers of overall patient satisfaction.
3.	Are the benefits worth the costs and potential risks?	Unknown, since no cost-benefit analysis exists, although ease of administration of therapeutic hypothermia coupled with lack of any other effective alternatives suggests this treatment should be the standard or care pending further effectiveness and optimal methods research.

## **Limitations**

- 1) No validated quality assessment tool to grade the evidence (Jadad scale).**
- 2) No statistical assessment of heterogeneity.**
- 3) No Quality of Life outcomes assessment.**

## **Bottom Line**

**Three small, adequately powered controlled trials with heterogeneous patient populations, cooling methods, and random allocation schemes consistently demonstrate improved neurologically intact hospital-discharge and six-month survival in ventricular fibrillation cardiac arrest comatose survivors who are immediately treated with hypothermia to 32-35° C for 4-24 hours with NNT = 6. Confidence Intervals are impressively narrow. This neurological recovery benefit is maintained when controlling for confounding variables including patient-specific characteristics (age, time to ROSC), method of cooling and center in which treatment occurred. Future research should assess quality of life measures and delineate the optimal method and duration of therapeutic hypothermia.**

