Critical Review Form
Therapy

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia, *N Engl J Med* 2002;346:557-563

Objective: "To compare the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest".

Methods: Randomized controlled trial involving four Melbourne, Australia ED's between September 1996 and June 1999. To accommodate various pre-hospital provider services, randomization was by day of the month (odd-day hypothermia, even day standard therapy). Inclusion criteria included return of spontaneous circulation (ROSC) after VF arrest in men >18 yrs or women > 50 (in case they were pregnant) with persistent coma. They were excluded if epinephrine resistant hypotension <90 mm Hg, ICU bed not available at one of four participating hospitals or if an alternative source of coma (CVA, drug overdose, head trauma) was felt likely.

Standard therapy was quite interventional and included mechanical ventilation (midazolam, vecuronium), ABG-directed ventilatory modification to maintain arterial oxygen 100 mm Hg and CO_2 40 mm Hg. Epinephrine and nitroglycerine were used to maintain MAP 90-100 mm Hg. All patients received aspirin and lidocaine. Potassium levels were maintained at 4.0 mmol/L and glucose 180 mg/dL. All patients also had a PA-catheter placed (except where treating clinicians refused). Core body temperature was measured with a tympanic or bladder probe until PA catheter placement.

Therapeutic hypothermia (TH) occurred pre-hospital and in the ED by placing ice packs around the head, neck, torso, and limbs. 33°C was the target temperature and was maintained for 12-hours. Active re-warming began at 18-hours and usual ICU protocols ensured at 24-hours. Active life support was withdrawn for most patients who remained comatose at 72-hours.

When patients were ready for hospital discharge, their outcomes were assessed by a rehabilitation specialist blinded to the treatment group. The primary outcome

was "survival to hospital discharge with sufficiently good neurologic function to be send home or to a rehabilitation facility" (p 558). Logistic regression was used to calculate an adjusted odds ratio for good outcome. The study was originally powered to detect a 36% improvement difference in good outcomes favoring TH, but during the trial this was adjusted downward since the ST group displayed better outcomes than preliminary data had suggested.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, by day of the month. Note this is subject to bias and an inferior method of randomization (Subverting Randomization in Controlled Trials, *JAMA* 1995: 274: 1456-1458).
2.	Was randomization concealed (blinded)?	Not to subjects, families, or treating clinicians.
3.	Were patients analyzed in the groups to which they were randomized?	An intention to treat analysis is <u>not</u> clearly stated.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Table 1 (p 559) demonstrates a significantly higher proportion of ST subjects were male and benefited from bystander CPR.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes – therefore this study is subject to *recall bias* and *co-intervention bias*.
2.	Were clinicians aware of group allocation?	Yes – therefore this study is subject to *co-intervention bias.*
3.	Were outcome assessors aware of group allocation?	No – so *ascertainment bias* is minimized.
4.	Was follow-up complete?	No loss to follow-up is reported.

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• 84 subjects were eligible over 33 months, but 7 were excluded (for various reasons) leaving 77 with 43 randomized to TH and 34 to ST. Four TH had incomplete data since the EM physician did not cool them so only their presenting data was analyzed. • Cooling occurred at 0.9°C per hour. • TH subjects received epinephrine more often than ST (59% vs. 49%). • Glucose was higher in TH than ST, but K+, lactate, Cr, and arterial pH were unaffected. • For no disability at discharge NNT = 7; for "good outcome". NNT = 4.3. • For prevention of one-death NNT = 6 (p=0.145). • Patient's age and time to ROSC significantly affected the primary outcome. For each two-year age increase there was a 9% decreased likelihood of good outcome (OR=0.91 0.84-0.98, p=0.014) while for each additional 1.5 minutes until ROSC there was a 14% decreased likelihood of good outcome (OR 0.86, 0.78-0.94 p=0.001).

		• Adjusting for age and time to ROSC, logistic regression noted a marked improvement in "good outcome" with TH (OR 5.25 95% CI 1.47 – 18.76, p=011).

2.	How precise was the estimate of the treatment effect?	Wide - but still therapeutically impressive 95% CI (see above). The lower limits would not deter me from using this therapy.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, although women, cardiogenic shock and MI subjects very under-represented by design. Also, availability of ICU would impact similar management at BJH.
2.	Were all clinically important outcomes considered?	No Quality of Life assessment was conducted, although lacking neurological deficits is probably universally preferred to suffering injury limiting daily activity or functional independence which the CPC scale roughly estimates.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. Lacking any other effective alternatives and with ease of administrating lacking any demonstrated adverse effects benefits outweigh risks and costs.

Limitations

1) Insufficient randomization scheme.
2) Unblinded patients/families, but would be difficult to ethically blind.
3) Potential Hawthorne effect particularly given the improved survival in the ST group compared with their earlier pilot project (*Ann EM* 1997;30:146-153).
4) Uncertain whether discharge to rehabilitation facility should be weighted equally with discharge from hospital to home neurologically intact. Further details ought to be provided.

Bottom Line

For VF cardiac arrest survivors with coma, immediate pre-hospital external cooling with ice-packs to 33ºC improves intact neurological discharge home (NNT = 7), discharge to either home or rehab (NNT = 4) and non-significantly reduces death (NNT = 6). Age and increasing time to ROSC both negatively impact good outcomes, but TH remains a significant predictor of "good outcome" even when adjusted for increasing age and delayed ROSC. No significant adverse effect in hemodynamic status or labs was noted with TH in this population. Future studies will need to confirm these findings in heterogeneous cardiac arrest populations arriving to ED's lacking ready ICU availability.