Critical Review Form
Therapy

From evidence to clinical practice:
Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest, *Crit Care Med* **2006;34(7):1865-1873**

Objective:

"To assess whether TH (therapeutic hypothermia) could be implemented in critical care practice for the treatment of coma following out-of-hospital CA (cardiac arrest)". (p.1869). A secondary objective was to explore TH in subjects with shock of non-VF CA coma.

Methods:

Retrospective study from Lausanne University Hospital in Switzerland of a standard therapy group (6/99-5/02) compared with a therapeutic hypothermia (TH) group presenting from 6/02-9/04. Following the European EM model, out-of-hospital resuscitation was delivered by an ambulance team including a physician. Upon ED arrival critical care physicians assumed care. The only inclusion criteria were post-CA coma, although coma is not defined or referenced.

Standard Resuscitation (SR) was quite intensive: intra-arterial and central venous catheter, MAP maintained >75mm Hg, $Pa0_2$, 90-100mm Hg, $Paco_2$ 36-40mm Hg, blood glucose 108-144 mg/dL and for >60 minutes of volume-refractory hypotension requiring vasopressors, a PA catheter was placed. Norepinephrine was the vasopressor and dobutamine (for mixed venous oxygen saturation >65% and blood lactate <2.5 mmol/L) was the inotropic agent.

TH to 33ºC was induced using ice-packs on the neck, axillae, torso, and groins for 24-hours and then active re-warming with precautions for temperature not to exceed 37.5°C for 48 hrs thereafter. During TH patients were treated with sedation (midazolam), analgesia (fentanyl) and paralysis (vecuronium). TH was started immediately upon ED arrival.

Outcomes were assessed independently by two blinded physicians chart reviewers based upon hospital notes written just before discharge. Outcomes were assessed by the Glasgow –Pittsburgh Cerebral Performance categories (CPC):

CPC1 = conscious, alert, able to work and to lead a normal life.
CPC2 = conscious, able to work at part-time, independent daily activities.
CPC3 = conscious, but fully dependent upon others for daily support because of severely impaired cognitive function.
CPC4 = vegetative state.
CPC5 = death.

To adjust the estimated effect of TH or outcome adjusting for confounding variables like time from collapse until return of spontaneous circulation, initial rhythm, presence of shock, blood lactate, need for volume expansion inotropic agents or vasopressors, the authors performed multivariable logistic regression using backward elimination.

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?	No – this is a retrospective study.
2.	Was randomization concealed (blinded)?	Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Patients were not randomized.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes – as noted in Tables 1-2 (p 1867) VF and non-VF CA survivors had no significant differences, although the SR-group approached significance in increased age and time to ROSC ($p = 0.09$) in both groups. Note that the TH received significantly more fluids, pressors, and inotropic agents than SR (Fig 3, p 1870)
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 – neither blinded nor randomized.
2.	Were clinicians aware of group allocation?	Yes.
3.	Were outcome assessors aware of group allocation?	No. "Outcome was assessed blindly (i.e., without knowledge of whether TH had been applied) by two physicians who independently reviewed the reports of neurological examination made before hospital discharge". (p 1866).
4.	Was follow-up complete?	No lost to follow-up was reported.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 109 CA patients were analyzed including 86 VF and 23 non-VF. • Non-VF CA survivors had longer delay until ROSC (22' vs. 33', p<0.001), higher blood lactate levels (7.7 vs. 10.7 mmol/L), and higher percentage with shock (45.8% vs. 23.3%). • Median time to attain therapeutic hypothermia was 5-hours with improved efficiency noted with experience. • Outcomes in VF (Table 4)

	NNT w/ 95% CI	ARR
CPC 1	3.6 (2.4-11)	0.279
CPC 1 or 2	3.3 (2.1-10.4)	0.302
Survival	6.1 (2.8 - ∞)	0.163

- TH was safely applied to non-VF CA survivors but no demonstrable benefit was noted in any outcome in this underpowered subgroup.
- The time required to attain TH had no relationship to outcome.
- TH was beneficial in the subset of patients with shock (NNT = 3.4 for CPC 1 or 2 outcome, p = 0.027).
- No patient was left in a vegetative state and among non-survivors the interval between admission and death was comparable (4 days in TH, 3 days in SR, p = 0.71).
- Logistic regression analysis identified only two independent predictors as statistically significant for good outcome: treatment group (OR 5.56 95% CI 2-16 favoring TH) and time from collapse to ROSC (OR for each 5' interval 0.53). The maximal benefit of TH is seen when return of spontaneous circulation within 30' after CA.
- TH was associated with increased CK-MB for unknown reasons.

		• Infections and arrhythmias were <u>not</u> more common in TH and no other serious adverse events were reported.

2.	How precise was the estimate of the treatment effect?	The upper limits of NNT CI would not dissuade my use of this therapy. Therefore, the effects are sufficiently precise.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Pts were similar but the Swiss EM management model is completely at odds with our US-system. How would this TH management impact US ED cases managed by EP's with scarce ICU beds and constant over-crowding?
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. Given the relative ease of this intervention and lacking any other alternatives, the benefits outweigh the risks in this otherwise dismal pathological process. No formal cost-benefit analysis performed.

Limitations

1. **Retrospective chart review without any methods (refer to *Annals EM* 1996; 27: 305-308)**
2. **Failure to report NNT with 95% CI increases work for the reader (above NNT calculated from http://statpages.org/ctab2x2.html**
3. **Potential *Hawthorne–effect* if clinicians realized their post-TH interventions would be scrutinized/published or if the new management model otherwise altered their clinical behavior to benefit post-CA outcomes.**

Bottom Line

Compared with standard aggressive post VF CA resuscitation care therapeutic hypothermia to 33ºC by ice packs/cooling blankets significantly improves complete recovery (NNT 3.6) and survival (NNT 6.1) while decreasing LTCF admissions and not increasing post-arrest infections or dysrhythmias. Patients with refractory shock also benefit (NNT 3.4 for CPC 1 or 2 outcome), but asystole and PEA subjects do not benefit from TH. Patients with return of spontaneous circulation within 30-minutes benefit the most from TH. Finally, TH did not prolong end-of-life decisions.