Date: July 2014  
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ARTICLE:

- **Citation:** Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.

- **Country:** Australia (Melbourne)

- **Funding Sources:** No mention

PURPOSE:

- **Research Question(s):** No research questions overtly stated. The authors conducted a prospective, randomized, controlled trial comparing moderate induced hypothermia with normothermia in comatose survivors of out-of-hospital cardiac arrest.

- **Hypothesis:** No hypotheses are overtly stated.

DESIGN:

- **Study Design:** Randomized, controlled trial.

- **Dependent / outcome Variable(s):** **Primary Outcome Measure:** survival to hospital discharge with sufficiently good neurologic function to be sent home or to a rehab facility. **Secondary outcome measures** included the hemodynamic, biochemical, and hematologic effects of hypothermia.

- **Independent / research Variable:** Randomization to normothermia/standard care (37°C) or mild hypothermia (33°C).

SETTING / SUBJECTS:
• **Research Setting:** Prehospital/ambulance setting for initial resuscitation efforts and early cooling. Emergency department and then ICU for vigorous cooling & continued treatment.

• **Subjects:**
  - **Study population:** Out of hospital cardiac arrest patients (adult) with ROSC and coma following prehospital resuscitation efforts.
  - **Inclusion / Exclusion criteria:** **Inclusion:** initial cardiac rhythm of ventricular fibrillation at the time of ambulance arrival, successful return of spontaneous circulation, persistent coma after the return of spontaneous circulation, & transport to one of four study EDs. **Exclusion:** age of less than 18 for men and less than 50 for women (due to the possibility of pregnancy), cardiogenic shock (SBP >90mmHg despite epinephrine infusion), possible causes of coma other than cardiac arrest (drug overdose, head trauma, CVA). Patients were also excluded if there was not an available ICU bed at the participating hospital.

  - **Number (control / intervention groups):** N = 84, seven excluded (5 transferred from initial hospital to a non-participant ICU, two because next of kin refused informed consent). N = 77 for analysis; 43 hypothermia and 34 normothermia. Four hypothermia patients did not receive the treatment they were randomized to (3 physician error, 1 inadvertently warmed). One patient assigned to normothermia received moderate hypothermia (33°C) for a prolonged period during emergency angioplasty.

  - **Demographics:** See Table 1 Below . . .
**Attrition:** As noted above; seven excluded (5 transferred from initial hospital to a non-participant ICU, two because next of kin refused informed consent). Data were analyzed for patients receiving the wrong treatment at the ED level only, not for ICU admit, 6, 12, 18, or 24 hours post-ED.

**METHODS:**
- **Interventions:**
  Following ROSC, eligible patients randomized to normothermia or hypothermia by the day of the month (hypothermia on odd-numbered days).

**Hypothermia group:**
- Paramedics began cooling by removing clothing & applying cold packs to patient’s head & torso.
- Vigorous cooling in ED or ICU ASAP after arrival with cold packs until core temp. reaches 33°C.
- 33°C maintained for 12 hours while sedated with versed & vecuronium to prevent shivering.
At 18 hours, rewarming was begun x 6 hours with heated air blanket, sedation and neuromuscular blockers.

**Normothermia group:**
- Usual care in the field.
- Initially sedated & paralyzed on ED arrival but target core temp was 37°C.
- Passive re-warming used if mild spontaneous hypothermia developed.

**All patients:**
- Usual assessment, treatment, intubation upon ED arrival
- IV versed 2-5 mg
- IV vecuronium 8-12 mg
- ABGs used to adjust vent
- Thrombolytics as usual, unless contraindicated
- IV heparin when indicated
- IV lidocaine bolus & drip when indicated
- Potassium and insulin when indicated
- ASA for all
- Core body temp. monitored until pulmonary artery catheter placed
- All ECG, ABGs, lytes, glucose, CK/MB, lactate at baseline, and q 1-3 hours, and at 6, 12, 18, and 24 hours post arrival
- CBC on arrival, at 12 and 24 hours
- Hemodynamic data obtained 1-3, 6, 12, 18, and 24 hours post arrival (except 7 hypothermia and 11 normothermia pts. due to physician refusal in ICU – no pulmonary artery catheter for those)
- After 24 hours, all pts. followed usual care, ICU protocols.

**Study Groups:**
- Mild hypothermia as above (33°C target)
- Normothermia as above (37°C target)

**Instruments:**
- Not described, but pulmonary artery catheters, ECGs, Labs, cooling & heating tools

**Data Collection:**
- Primary outcome (survival and degree of neurologic impairment) assessed by specialist in rehab medicine blinded to treatment group
- Primary outcome assessed when ready for discharge from hospital
Secondary outcomes assessed at baseline, 6, 12, 18 and 24 hours (e.g. physiologic measures)

DATA ANALYSIS:
- **Level of Data:** Categorical  Ordinal  Interval

  Survival to hospital discharge (good or bad outcome) = categorical
  Vital signs, biochemical markers = continuous data (ordinal or interval level)

- **Statistics Used:**
  **Categorical variables** = chi-square or Fisher’s Exact Test (Fisher’s exact is really the same as chi-square to use when there are small numbers)
  **Continuous variables** = t-tests (compare the mean of two groups) or analysis of variance (compare the mean of more than two groups)
  **Adjusted odds ratios** – Odds ratios are the product of multivariate logistic regression (used to figure out the odds of a good outcome vs. a bad outcome)

- **What, if any, confounding variables were controlled for / adjusted for:**
  Multivariate analysis (logistic regression, controlling for multiple potential confounders) was used to control for baseline differences between the groups in age and time from collapse to ROSC. Both age and time from collapse to ROSC were identified in univariate (not controlling for other factors) analyses to be associated with the likelihood of a good outcome, so the investigators controlled for these factors in the multivariate analyses.

  These analyses are all appropriate for the types of data used.

RESULTS:
- **Brief answers to research questions:**
  - 21/43 (49%) of hypothermia patients survived with a “good” outcome vs. 9/34 (26%) in the normothermia group.
  - Odds ratio for good outcome with hypothermia (vs. with normothermia) = 5.25 (95% CI: 1.47 – 18.76), \( p = 0.011 \). (After adjusting for confounders)
  - Hypothermia was associated with lower cardiac index, higher systemic vascular resistance, and hyperglycemia.
  - No difference in adverse events between the groups.

- **Additional findings:**
  As above.
Other possible explanation for findings:
- There was a potential for bias as clinicians could not be blinded to the patient’s study group. It is possible that care could have been delivered differently to the two groups of patient due to this lack of blinding. The investigators did use protocolized care when possible to try to minimize the possibility that this could have happened.

Limitations:
- Not feasible to blind clinicians to patient’s treatment groups, so clinicians might have introduced bias through the care they provided. Protocols were used in an attempt to mitigate this.
- Unlikely that therapy was withdrawn inappropriately as decisions to withdraw care were made by multidisciplinary team & family.
- Difficulty with out-of-hospital randomization, odd & even day schedule used due to many ambulances & 4 EDs involved.
- Patients with a poor prognosis were excluded.
- Where discharged to was used as primary outcome despite the fact that some patients may be discharged to a nursing home due to a lack of social support (as opposed to having a bad neurological outcome).
- It is notable that the confidence interval around the multivariate adjusted odds ratio is quite wide. The authors noted (p.558, last paragraph of the statistical analysis section) that there was some difficulty with obtaining an adequate sample (the trial had to be extended to enroll additional patients) as the normothermia patients had a better “good” outcome rate than had been previously published and used for the initial sample size calculation. In the end, they determined that they needed at least 31 patients in each group and had just that in the normothermic group. Some patients received the treatment they were not randomized to (four hypothermic and one normothermic) and they were not analyzed with the groups they were assigned to (as in an intention-to-treat analysis) but were rather only analyzed at baseline (ED arrival) and discharge, not for the 6, 12, 18, and 24 hour outcomes.

IMPLICATIONS FOR PRACTICE:
- Applicable to this clinical practice: Very relevant and applicable to practice here.
- Feasibility (cost, resources, etc): Possibly difficult to begin cooling in the prehospital and ED settings on a widespread basis.
• **Clinically Relevant**: An important clinical problem with uncertainty regarding the best temperature to cool to and the best duration of cooling remaining.

**LEVEL OF EVIDENCE / DECISION FOR USE:**

- **Background**  
  **Consider Replication**  
  Ready for use

  - It would be helpful if this study could be repeated with another population to ensure that these findings were not influenced by bias introduced by the lack of blinding.
  - It would also be helpful if the study were repeated in a larger sample as the confidence interval around the multivariate, adjusted odds ratio for the primary outcome (good outcome at discharge) was quite wide and there were difficulties with the initial sample size calculation and crossover between the groups.

- **Level of Evidence**:
  - Ia Evidence obtained from meta-analysis of randomized controlled trials
  - Ib Evidence obtained from at least one RCT
  - IIa Evidence obtained from at least one well-designed controlled study without randomization
  - IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
  - III Well-designed non-experimental studies
  - IV Expert committee reports, opinions of experts