UAMS Journal Club
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Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest

Clinical Bottom Line

Hypothermia is not associated with better outcomes in terms of mortality or neurological function compared with normothermia in patients with out-of-hospital cardiac arrest and actually is associated with a higher risk for arrhythmias.

PICO Question

Is hypothermia superior to normothermia in the outcomes of out-of-hospital cardiac arrest?

P - Patients presenting to the hospital with out-of-hospital cardiac arrest with ROSC achieved
I - Targeted temperature management of hypothermia
C - Targeted temperature management of normothermia
O - Mortality rates and healthy quality as measured by neurologic disability after 6 months

Background

Fever as been proposed as a risk factor for unfavorable neurological outcomes in patients following cardiac arrest. Because of this, targeted temperature management is the current recommendation for these patients to prevent hypoxic-ischemic brain damage. Previous trials have suggested increased survival and improved neurological outcome in patients who underwent hypothermia at 33 degrees Celsius vs normothermia, however overall evidence is still of low certainty.

Paper 1:

Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2021;384(24):2283-2294. doi:10.1056/NEJMoa2100591

Pubmed link:https://pubmed.ncbi.nlm.nih.gov/34133859/

The Basics

This was an open-label, RCT done in 2021 in Sweden that investigated targeted temperature management in patients after cardiac arrest. This study had two groups, a normothermia group and a hypothermia group. The intervention period was 40 hours long; normothermia group was maintained at a temp of 37.5 or less and the normothermia group was kept at 33 for 28 hours and then rewarmed to 37. In either group, cooling was initiated if febrile (over 37.8). Mortality after 6 months was measured as the primary outcome and functional outcome as defined by the Rankin score was the secondary outcome.

Inclusion Criteria

- Adults $\geq$ 18 years old who were admitted to the hospital after out-of-hospital cardiac arrest of a presumed cardiac or unknown cause irrespective of initial rhythm.
- Unconscious and not able to obey verbal commands (<4 score on the Full Outline of Unresponsiveness) and no verbal response to pain

- More than 20 minutes of spontaneous circulation after resuscitation

Exclusion Criteria

- Interval from ROSC to screening of more than 180 minutes
- Unwitnessed cardiac arrest with systole as initial rhythm

Primary Outcome
Mortality at 6 months

Secondary Outcome
Functional outcome as assessed by Modified Rankin Scale Score 4-6 (moderately-severe to severe disability or worse)

Results
There was no significant difference between the two groups with respect to death and poor functional outcome at 6 months. The distribution of scores on the modified Rankin scale between the groups was similar, as was health- related quality of life. The results were consistent in the analysis of survival and in pre-specified subgroups.

Limitations

- Isolating the effect of hypothermia was done by treating both trial groups the same other than temperature management, and the standard treatment in the ICU might not necessarily be representative of clinical practice. The protocol for the assessment of neurological prognosis and guidance for withdrawal of life support was conservative and may have influenced outcomes.
- Staff members in the ICU were aware of the assigned target temperature due to logistical issues of blinding this, but bias was minimized by blinding the assignments to the investigators, statisticians, and authors of the study.
- There was no control group without temperature management.
- The patient population was limited to out-of-hospital cardiac arrest so the results are not fully applicable to other presentations of cardiac arrest.

Paper 2: Meta-analysis

Elbadawi A, Sedhom R, Baig B, et al. Targeted Hypothermia vs Targeted Normothermia in Survivors of Cardiac Arrest: A Systematic Review and Meta-Analysis of Randomized Trials. *Am J Med*. 2022;135(5):626-633.e4. doi:10.1016/j.amjmed.2021.11.014

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/34958763/

The Basics
Systematic review and meta-analysis of 8 RCTs including a total of 2927 patients comparing targeted temperature management versus target normothermia. (including trials with targets from 31.7C to 34C).

Search Methods

All studies in MEDLINE, EMBASE or Cochrane database that evaluated targeted hypothermia versus normothermia among comatose survivors of cardiac arrest with shockable or non-shockable rhythms including studies evaluating any degree of hypothermia.

Exclusion Criteria

- Both groups received hypothermia
- Hypothermia during CPR
- Studies not reporting survival or neurologic recovery
- Non-randomized studies

Primary Outcome
Mortality and neurologic recovery at the longest reported follow-up.

Secondary Outcome
In-hospital mortality, ventricular arrhythmias, sepsis and pneumonia.

Limitations

- Interventions slightly varied with different temperature targets and cooling methods
- Different subpopulations including witness only or types of arrest (Vfib/Vtach vs PEA, etc)
- Different placebo arms: Target normothermia not practiced in early studies

Results
There was no significant difference between the two groups with respect to mortality at longest reported follow up (95% [CI] 0.87-1.06). There was no difference in favorable neurologic outcome (CI 0.99-1.73), in-hospital mortality (CI 0.77-1.01), or other secondary outcomes other than arrhythmias. Ventricular arrhythmias were more common in the hypothermia group (RR 1.36 and CI 1.17-1.58).