TTM for Cardiac Arrest with Nonshockable Rhythms


Background
- 2015 ILCOR Guidelines recommend TTM (32C to 36C) for all patients with coma after resuscitation from cardiac arrest.
- Nonshockable rhythms are now predominant among cardiac arrest patients and are associated with a poor prognosis (2-15% of patients have a good neurologic outcome)
- Use of TTM in patients with nonshockable rhythms (asystole or PEA) has shown inconclusive effects across limited studies.
  - Post-hoc analysis of Nielsen et al TTM trial did not demonstrate benefit of TTM in patients with nonshockable rhythms
  - Chan, et al. JAMA 2016: suggested harm
  - Mader, et al. Ther Hypothermia Temp Manag 2014: suggested harm
- Also, the use and benefit of TTM in patients with cardiac arrest due to a noncardiac cause is uncertain.

Objective – The HYPERION Trial
- Assess whether moderate therapeutic hypothermia at 33C, as compared with targeted normothermia at 37C, would improve neurologic outcome in patients with coma who were successfully resuscitated from cardiac arrest with a nonshockable rhythm.

Study
- Investigator-initiated, open-label, blinded-outcome-assessor, pragmatic, multicenter, randomized controlled trial
- 25 ICUs in France (11 university hospitals; 14 community hospitals)
- Patients
  - Included
    - Adults ≥ 18 years of age
    - Resuscitated from OHCA or IHCA
    - Nonshockable rhythm due to any cause
    - Coma (GCS ≤ 8) at ICU admission
  - Excluded
    - No-flow time of more than 10 min before CPR
    - Low-flow time of more than 60 min from time of CPR to ROSC
    - Hemodynamic instability (NE or epi infusion > 1 mcg/kg/min)
- Moribund condition
- Severe hepatic dysfunction
- Pregnancy
- Inmate or under guardianship
- Lack of health insurance
- Next of kin for the patient declined to participate

- Randomized
  - 1:1
  - Moderate therapeutic hypothermia group
    - Target 33°C
    - Maintained for 24 hours
    - Each center followed its own protocol
      - Active internal cooling with a device
      - Active external cooling with a device
      - Active external cooling without a device
    - Slow rewarming to 36.5-37.5°C maintained over 24 hours
    - Sedation and NMBA administered according to each center’s protocol
  - Normothermia group
    - Target 36.5-37.5°C
    - Maintained for 48 hours
    - Sedation given routinely only during first 12 hours after randomization

- Primary Outcome
  - Survival with favorable 90-day neurologic outcome (assessed using CPC and defined as a CPC of 1 or 2)
  - Assessed using a semi-structured telephone interview

- Secondary Outcomes
  - Mortality
  - Mechanical ventilation duration
  - ICU and hospital LOS
  - Infection
  - Adverse events

**Results**
- 584 patients underwent randomization – **581 patients in final analysis**
  - Moderate hypothermia group: 284 patients
  - Normothermia group: 297 patients
  - Characteristics evenly balanced between the two groups
  - Case of cardiac arrest was noncardiac in two-thirds of patients
  - Circulatory shock present in almost 60%
  - Most common cause of death – withdrawal of life support

- Temperature Management
  - Moderate hypothermia group
    - Began about 16 min after randomization
    - Intravascular catheter used in about 15%
    - Closed loop surface cooling device in 47.9%
    - Basic external cooling device with no closed loop in 37%
    - Mean temperature between 12-24 hours was 33.5°C
- Normothermia group
  - Intravascular catheter used in about 15%
  - Closed loop surface cooling device in 34%
  - Basic external cooling device with no closed loop in 51%
  - Mean temperature between 12-24 hours was 37°C

- Primary Outcome – Favorable neurologic survival at 90-days
  - Moderate hypothermia group: 10.2%
  - Normothermia group: 5.7%
  - P=0.04

- Secondary Outcomes
  - Mortality
    - Moderate hypothermia group: 81.3%
    - Normothermia group: 83.2%
  - Duration of mechanical ventilation – no difference
  - ICU LOS – no difference
  - Adverse events – no difference

Limitations as described by Authors
- Primary outcome assessed using a telephone interview rather than face-to-face interview
- Substantial portion of patients had body temps above 38°C in the period after TTM
- Used TTM for 56-64 hours in the hypothermia group and in 48 hours in the normothermia group to avoid rebound hyperthermia
- Fragility Index value for the study was 1 – suggests that an outcome change in 1 patient could make the difference in primary outcome results nonsignificant

Take Home Points
- Use of moderate hypothermia at 33°C led to higher percentage of patients who survived with favorable neurologic outcome at 90 days.
- NNT from this trial is 22, to achieve a CPC of 1 or 2 with TTM in patients with a nonshockable rhythm.