TTM for Cardiac Arrest with Nonshockable Rhythms

Key Article: *Lascarrou JB, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019. [epub ahead of print]*

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
    - Testori, et al. Resuscitation 2011: beneficial effect
    - Perman, et al. Circulation 2015: beneficial effect
    - Vaahersalo, et al. Intensive Care Med 2013: no effect
    - Dumas, et al. Circulation 2011: no effect
    - 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 $\geq$ 18 years of age
        - Resuscitated from OHCA or IHCA
        - Nonshockable rhythm due to any cause
        - Coma (GCS $\leq$ 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 33C
        - 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 36.5-37.5C maintained over 24 hours
        - Sedation and NMBA administered according to each center's protocol
    - Normothermia group
        - Target 36.5-37.5C
        - 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 33.5C

    - 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 37C
- 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 38C 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 33C 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.