Targeted Temperature Management in Post Cardiac Arrest Patients

Treesa Joseph, PharmD
PGY-1 Pharmacy Resident
Atlantic Health System

Continuing Education Presentation
June 15th, 2017
Objectives

- Explain the rationale behind the process of post cardiac arrest Targeted Temperature Management (TTM)
- Explain the evidence-based recommendations for the use of medications during the TTM process
- List the major side effects of each medication recommended for use in post cardiac arrest TTM
Post Cardiac Arrest Care

American Heart Association:

- All comatose adult patients who attain return of spontaneous circulation (ROSC) undergo targeted temperature management (TTM)

- Cerebral perfusion scores significantly improved in patients who underwent TTM
Post Cardiac Arrest Care

2015 Recommendations- Highlights

▪ Comatose adult patients with ROSC after out-of-hospital ventricular fibrillation (VF) or ventricular tachycardia (VT) cardiac arrest should be cooled to 32°C to 36°C
  • Class I, (LOE B-R)

▪ Comatose adult patients with ROSC after out-of-hospital with non VF/VT (non shockable) cardiac arrest or in hospital cardiac arrest should be cooled to 32°C to 36°C
  • Class I, (LOE C-EO)

LOE= Level of evidence
R= based on randomized studies
EO= based on consensus of expert opinions

Overview

Adult Immediate Post-Cardiac Arrest Care Algorithm — 2015 Update

1. Return of spontaneous circulation (ROSC)
   - Optimize ventilation and oxygenation
     - Maintain oxygen saturation ≥ 94%
     - Consider advanced airway and waveform capnography
     - Do not hyperventilate
   - Treat hypotension (SBP < 90 mm Hg)
     - IV/O bolus
     - Vasopressor infusion
     - Consider treatable causes

2. 12-Lead ECG: STEMI or high suspicion of AMI
   - Yes: Coronary reperfusion
   - No: Follow commands?

3. Initiate targeted temperature management

4. No: Follow commands?
   - Yes: Advanced critical care

5. Doses/Details
   - Ventilation/oxygenation:
     - Avoid excessive ventilation.
     - Start at 10 breaths/min and titrate to target PETCO₂ of 35-40 mm Hg.
     - When feasible, titrate FiO₂ to minimum necessary to achieve Spo₂ ≥ 94%.
   - IV bolus:
     - Approximately 1-2 L normal saline or lactated Ringer's
   - Epinephrine IV infusion:
     - 0.1-0.5 mcg/kg per minute (in 70-kg adult: 7-35 mcg per minute)
   - Dopamine IV infusion:
     - 5-10 mcg/kg per minute
   - Norepinephrine IV infusion:
     - 0.1-0.5 mcg/kg per minute (in 70-kg adult: 7-35 mcg per minute)

Reversible Causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary
Post Cardiac Arrest Care

Cardiac Arrest
- Decreased systemic perfusion - decreased cerebral oxygen delivery
- Anoxic brain tissue - cerebral edema

Neurological Deficits

Reperfusion
- Exacerbates cerebral edema
- Alters inflammatory response
- Further tissue injury

Compromised neurological function

Targeted Temperature Management (TTM)

Targeted temperature management previously known as therapeutic hypothermia

- Active treatment to achieve and maintain a specific temperature (between 32°C and 36°C)
- Goal to preserve neurological function
Mechanism of TTM

Targeted Temperature Management

- Slows cerebral metabolism
- Decreases oxygen consumption
- Lessens cerebral edema

# Landmark Trials

➢ Improved neurological outcomes and mortality in comatose patients with out-of-hospital cardiac arrest

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Outcome</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard S et al 2002</td>
<td>n=77; RCT, un-blinded trial</td>
<td>Survival to discharge with good neurological outcome 49% vs 26% (p=0.046, NNT=4)</td>
<td>Improved the incidence of favorable discharge disposition</td>
</tr>
<tr>
<td>Holzer M et al (HACA Trial) 2002</td>
<td>n=136; RCT, multicenter</td>
<td>Favorable neurologic outcome within 6 months 55% vs. 39% (RR 1.40; 95% CI 1.08-1.81; p=0.009)</td>
<td>Therapeutic mild hypothermia increased rate of favorable outcome.</td>
</tr>
</tbody>
</table>

RCT=Randomized Controlled Trial  
NNT=Number needed to treat  
CI=Confidence Interval  
RR=Relative Risk

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Landmark Trials

Nielsen N et al (*TTM trial*) 2013
- TTM at 33°C vs 36°C for 24 hours

<table>
<thead>
<tr>
<th>Outcome</th>
<th>33°C Group</th>
<th>36°C Group</th>
<th>Hazard Ratio or Risk Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: deaths at end of trial</td>
<td>235/473 (50)</td>
<td>225/466 (48)</td>
<td>1.06 (0.89–1.28)</td>
<td>0.51</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic function at follow-up†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPC of 3–5</td>
<td>251/469 (54)</td>
<td>242/464 (52)</td>
<td>1.02 (0.88–1.16)</td>
<td>0.78</td>
</tr>
<tr>
<td>Modified Rankin scale score of 4–6</td>
<td>245/469 (52)</td>
<td>239/464 (52)</td>
<td>1.01 (0.89–1.14)</td>
<td>0.87</td>
</tr>
<tr>
<td>Deaths at 180 days</td>
<td>226/473 (48)</td>
<td>220/466 (47)</td>
<td>1.01 (0.87–1.15)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

- Cooling to 33°C vs 36°C did not provide any additional benefit

Landmark Trials

Common misconception

- ‘TTM trial showed no benefit with TTM’

TTM trial

- Both groups received active cooling
- Comparison between two target temperatures (33°C vs 36°C)
- High bystander CPR (shorter “no flow” time)

Pop Quiz!

- Patients undergoing targeted temperature management post cardiac arrest are recommended to be cooled to:
  
  a. 30°C  
  b. 32°C - 36°C  
  c. 25°C - 30°C  
  d. All of the above  
  e. None of the above
Pop Quiz!

❖ Patients undergoing targeted temperature management post cardiac arrest are recommended to be cooled to:

a. 30°C
b. 32°C - 36°C
c. 25°C - 30°C
d. All of the above
e. None of the above
Ideal Temperature Target

Nielsen et al

- 33°C vs 36°C offered no additional benefit
- Did not show any additional adverse effects when cooled to 33°C
  - Any adverse events (93% vs 90%; p=0.86)
- No clinical or statistically significant differences in patient outcomes

➢ Due to lack of significant data, either temperature goal (33°C or 36°C) seem reasonable.
  - Patient specific temperature targets

## Initiation of TTM: Optimal time

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<tr>
<td>Mooney et al 2011</td>
<td>n=140; case review, multicenter</td>
<td>Survival to elapsed time from ROSC to imitation of cooling</td>
<td>For every hour delay in cooling risk of death increases by 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative hazard estimate: 1.20 (95% CI 1.04-1.39)</td>
<td></td>
</tr>
</tbody>
</table>

- **TTM is a medical emergency!**

Relative Contraindications of TTM

- Active uncontrolled bleeding
- Follows verbal commands
- Recent surgery
- Known or suspected septic shock
- Arrhythmias/QTc prolongation
- More than 6 hours after ROSC

Temperature Management Overview

- **Induction**
  - 32°C or 36°C

- **Maintenance**
  - Maintaining the target temperature

- **Rewarming**
  - 0.25°C/hour until temp reaches 36°C

0-8 hours  
24 hours  
48 hours

Pop Quiz!

- Targeted temperature is achieved by which of the following ways
  a. Cooling blanket
  b. Infusing cold 0.9% sodium chloride
  c. Keeping the patient in a refrigerator
  d. A & B
  e. All of the above
Pop Quiz!

- Targeted temperature is achieved by which of the following ways
  a. Cooling blanket
  b. Infusing cold 0.9% sodium chloride
  c. Keeping the patient in a refrigerator
  d. A & B
  e. All of the above
Methods to Institute TTM

Conventional cooling techniques
  ▪ Cold saline, crushed ice or ice bags

Surface cooling systems
  ▪ Moving cold fluid or cold air through blanket of pads wrapped around the patient.
  ▪ Cooling blankets and surface pads

Intravascular cooling systems
  ▪ Circulating cool or warm saline in a closed loop through a catheter’s balloon
  ▪ Catheter balloons: Femoral, jugular, subclavian

Methods to Institute TTM

Surface vs Intravascular cooling
Methods to Institute TTM

Gillies M et al.

- **Objective:** Surface vs Endovascular cooling
- **Study design:** Retrospective cohort study, n= 83
- **Outcomes:**
  - Less temperature variation in endovascular group
    - Between 10 hour and 20 hour of cooling (1.0 vs 1.7; p=0.003)
  - No difference in outcomes:
    - Hospital mortality (54.2% vs 50.0%; p=0.51)
    - Poor neurological outcomes (59% vs 57.1%; p=0.82)

Induction Phase
Induction Phase

Hemodynamic Stability

- No specific MAP or SBP targets
  - Published protocols recommend to maintain MAP at 65 mmHg or SBP above 80 mmHg
  - SBP <80 mmHg
    - Norepinephrine
      - 0.1–0.5 mcg/kg/min (In a 70 kg adult, 7–35 mcg/min)
  - Symptomatic Bradycardia
    - Dopamine
      - 5–10 mcg/kg/min
    - May tolerate HR 30-40 bpm!!!
    - Overstimulation of heart rate can decrease myocardial contractility

SBP: Systolic blood pressure
MAP: Mean arterial pressure
Induction Phase

Goals

▪ Monitor for seizures
▪ Optimize analgosedation
▪ Minimize metabolic demand
  • Paralytics
  • Shivering prevention

**Induction Phase**

**Seizures**

- Common, occurs in one-third of the patients post cardiac arrest
- Routine seizure prophylaxis in post cardiac arrest patients
  - Not recommended
  - Increased risk of side effects

- *Monitoring may include continuous/intermittent Electroencephalography (EEG) or Bispectral Index (BIS)*

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Sedation and Analgesia

Animal studies have shown:
- Inadequate sedation leads to partial or complete loss of protective effects of TTM

Goals:
- Optimize angalgosedation
  - Prior to initiation of pharmacologic paralytic
- Minimize doses of sedatives and analgesia
  - Hypothermia reduces clearance
- Select agents with short half-life
  - Enables early prognostication

Sedation and Analgesia

Fentanyl IV

- Opioid analgesic; provides sedation and analgesia
- 100 x potent than morphine, fast onset of action (0-2 seconds)

- Metabolized by liver; decrease in hepatic blood flow

- Adverse effects
  - Respiratory depression
  - Chest wall rigidity with bolus administration
  - Ileus

Fritz H et al & Zhou et al

- Hypothermia decreases systemic clearance

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Sedation and Analgesia

Propofol

- Sedative
- Fast onset (10 seconds) and offset of action (3-10 minutes)
- Decreases
  - Cerebral metabolic oxygen demand
  - Shivering threshold

- Adverse effects: Hypotension, bradycardia, propofol infusion syndrome, hypertriglyceridemia

Zhou et al

- Clearance of propofol decreased by 25% compared to normothermia conditions
  - 0.59 (95% CI: 0.24–1.38) L/min vs 0.79 (0.58–1.08) L/min

Sedation and Analgesia

Midazolam

- Benzodiazepine; provides sedation and amnesia
- Sedative impact on brain provides shiver control
- Onset of action (15 minutes); duration of action (<2 hours)
- Active metabolite: 1-hydroxymidazolam

- Adverse effects: Respiratory depression, bradypnea

- Accumulation of active metabolite in renal impairment; prolonged sedation

Pop Quiz!

- A 50 year old post cardiac arrest patient is ordered cisatracurium while being started on external cooling pads to attain a temperature of 33ºC. What sedative would you recommend in this hemodynamically stable patient based on pharmacokinetic data available in patients undergoing TTM?

  a. Propofol  
  b. Pentobarbital  
  c. Dexmedetomidine  
  d. Midazolam  
  e. None of the above
Pop Quiz!

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a. Propofol
b. Pentobarbital
c. Dexmedetomidine
d. Midazolam
e. None of the above
Neuromuscular blockers (NMB)

- Achieve target temperature quicker
- Quickest method to cease shivering
  - Useful in hemodynamically unstable patients

Caveats to Use

- Train-of-four (TOF) unreliable
  - Decreased peripheral nerve conduction
- Mask seizures
  - Continuous EEG monitoring is recommended


Neuromuscular blockers (NMB)

2016 Critical care guideline recommendations:
- No recommendation for routine use in TTM
- Suggest NMBs can be used to manage overt shivering during TTM

Task force good practice statement:
- Assessment of degree of blockade
  - Peripheral nerve stimulation + clinical assessment (ventilator triggering, degree of shivering)
- Protocol guided NMB use in patients undergoing therapeutic hypothermia
- Adequate analgesia and sedation prior to and during neuromuscular blockade.

Neuromuscular blockers (NMB)

- Salciccioli et al
  - **Objective:** Continuous NMB for 24 hours and outcomes in OHCA
  - **Study design:** n=111, A post hoc analysis, prospective observation study
  - **Outcomes:**
    - Increase in crude survival rate with continuous NMB use
      - 78% vs 41%; p = 0.004
    - Post multivariate adjustment
      - OR: 7.23, 95% CI: 1.56-33.38
    - Showed improved lactate clearance

OR: Odds ratio
CI: Confidence interval
OHCA: Out of hospital cardiac arrest

Neuromuscular blockers (NMB)

- Lascarrou et al.
  - **Objective:** Effect of NMB on neurological outcomes and incidence of pneumonia
  - **Study design:** Observational retrospective study, n = 144
  - **Outcomes:**
    - No statistically significant difference in neurological outcomes after 3 months in NMB group
      - 42% vs. 36%, p = 0.26
    - Early-onset pneumonia higher in NMB group
      - 64% vs. 33%; p = 0.005; after adjustment for propensity scores; no difference

Neuromuscular blockers (NMB)

Cisatracurium

- Neuromuscular blocker; given only after sedation
- Eliminated through urine
  - Accumulation with renal impairment

Adverse effects:

- May mask insufficient sedation and/or seizures
- Neuropathy and prolonged weakness

*Alternative Agent:*

Vecuronium

- Active metabolite: 3-desacetyl vecuronium
- Rate of elimination decreased in hepatic dysfunction
  - Significant increase in duration of action
Maintenance Phase
Post Cardiac Arrest Care

2015 Recommendations- Highlights

- Hypothermia (TTM) post cardiac arrest *should be maintained* for at least 24 hours after achieving target temperature.
  - Class IIa, (LOE C-EO)
- Reasonable to actively prevent fever in comatose patients after TTM.
  - (Class IIb, LOE C-LD)

LOE= Level of evidence
EO= based on consensus of expert opinions
Shivering Pathophysiology

- Human body maintains a core temperature: 36.4°C +/- 0.4°C
- Shivering:
  - Involuntary response to enhance heat production
  - Resulting in an increase in oxygen consumption

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Bedside Shivering Assessment Scale

- Bedside Shivering Assessment Scale (BSAS)
  - Quick assessment to identify shivering in patients

<table>
<thead>
<tr>
<th>Score</th>
<th>Type of shivering</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>No shivering is detected on palpation of the masseter, neck, or chest muscles</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>Shivering localized to the neck and thorax only</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Shivering involves gross movement of the upper extremities (in addition to neck and thorax)</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Shivering involves gross movements of the trunk and upper and lower extremities</td>
</tr>
</tbody>
</table>

- Frequent shivering assessment is required in the induction phase

Pharmacologic Management

Widen interthreshold range
- Lowering vasoconstriction and shivering threshold
- Raising vasodilation and sweating thresholds

- Pharmacologic agents:
  - Acetaminophen
  - Buspirone
  - Dexmedetomidine
  - Meperidine
  - Magnesium

Pharmacologic Management

Acetaminophen

- Inhibition of cyclooxygenase-mediated prostaglandin synthesis
- Lowers hypothalamic set-point
- Provides analgesia

Studies showed high dose acetaminophen (4-6 g /day) decreased body temperature by 0.3°C – 0.4°C

Adverse effects: Liver toxicity

Note: Dose reduction or discontinuation in hepatic impairment patients

Pharmacologic Management

Buspirone

- Acts centrally as 5 HT1 receptor agonist to decrease shivering threshold

Mokhtarani et al showed that combination of buspirone and meperidine caused little sedation or respiratory adverse effects

- Shivering thresholds:

<table>
<thead>
<tr>
<th>Buspirone 60mg</th>
<th>Buspirone 30mg + low dose Meperidine (serum conc 0.4mcg/mL)</th>
<th>High dose Meperidine (Serum conc 0.8mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35°C +/- 0.8°C</td>
<td>33.4°C +/- 0.7°C</td>
<td>33.4°C +/- 0.7°C</td>
</tr>
</tbody>
</table>

Adverse effects: Hypotension, nausea

Pharmacologic Management

Buspirone and Dexmedetomidine

- Buspirone (5 HT1 receptor agonist), Dexmedetomidine (α2-agonist)

Lenhardt R et al showed buspirone and dexmedetomidine synergistically reduced shivering threshold.

- Shivering thresholds: (p<0.01)
  - Control: 36.4°C +/- 0.5°C
  - Buspirone only: 34.9°C +/-0.6°C
  - Dexmedetomidine only: 36.1°C +/- 0.6°C
  - Combination: 34.2°C +/- 0.5°C
Pharmacologic Management

Meperidine IV

- K-opioid receptors and \( \alpha_2 \) adrenergic receptors

Kurz A et al showed

- Reduced shivering threshold nearly twice as much as the vasoconstriction threshold
  - \((6.1^\circ C \pm 3.0^\circ C \text{ and } 3.3^\circ C \pm 1.5^\circ C, p = 0.001)\)

Adverse effects: Somnolence, seizures, hypotension, seizures

Kurz A et al Meperidine Decreases the Shivering Threshold Twice as Much as the Vasoconstriction Threshold Anesthesiology 5 1997, Vol.86, 1046-1054
Pharmacologic Management

Magnesium Sulfate

- Peripheral vasodilation – decrease time to goal temperature

Zwelfler et al

- Magnesium + Meperidine vs Meperidine containing other regimens in healthy patients cooled to 31°C
- Showed that the magnesium group
  » Higher comfort scores (p < 0.001)
  » No adverse events associated with addition of magnesium
  » Vasodilation: 88% vs 29% (p = 0.02)

Adverse effects: Hypotension, heart block, CNS depression
Pop Quiz!

❖ What is the major side effect we need to monitor for a patient receiving meperidine during TTM?

a. Seizure  
b. Shivering  
c. Hypertension  
d. None of the above
Pop Quiz!

❖ What is the major side effect we need to monitor for a patient receiving meperidine during TTM?

a. Seizure
b. Shivering
c. Hypertension
d. None of the above
Rewarming Phase
Post Cardiac Arrest Care

2015 Recommendations - Highlights

▪ Reasonable to actively prevent fever in comatose patients after TTM
  • (Class IIb, LOE C-LD)

24 hours after TTM start time

▪ Goal:
  • Rewarm to 36.5°C at a rate of 0.25°C/hour
  • Actively maintain temperature at 36.5°C for 24 hours
  • Passively maintain normothermia for next 48 hours

LOE=Level of evidence
EO= based on consensus of expert opinions
Rewarming Phase

Post–cooling Fever

Bro-Jeppesen et al

- **Objective:** 30 day mortality in patients with post-cooling fever vs no fever
- **Study design:** Prospective, observational, cohort study, n = 270
- **Outcomes:**
  - 30 day mortality
    - Adjusted hazard rate (HR):1.8 (95% CI: 1.1-2.7, *p*=0.02)
  - Good neurological outcomes
    - (61% vs 75%, *p*=0.02)

ICU Management

Electrolyte management

- Monitor levels:
  - Magnesium, potassium, calcium and phosphorus

- During TTM:
  - Dysrhythmias: low magnesium and potassium
  - Replace potassium: <3.5mEq/L

- Post TTM:
  - Elevation in electrolyte levels due to shifting of electrolytes
  - Increased hyperkalemia risk

ICU Management

Hyperglycemia
- Decreased insulin sensitivity and secretion
- Negative neurological outcomes seen with hyperglycemia
- Management: Initiate continuous intravenous insulin
  - Monitor glucose levels closely

Venous Thromboembolism (VTE) Prophylaxis
- Assess patients coagulation need appropriately
- Avoid SUBQ administration

Stress Ulcer Prophylaxis
- Follow institutional policy
Pop Quiz!

❖ The rationale for cooling patients post cardiac arrest is:

a. To preserve neurologic function  
b. To allow heart to rest and recover  
c. To allow patients body to recover from shock  
d. None of the above
Pop Quiz!

The rationale for cooling patients post cardiac arrest is:

a. To preserve neurologic function
b. To allow heart to rest and recover
c. To allow patients body to recover from shock
d. None of the above
Pharmacist Impact

- High risk medication classes
- Potentially uncommon medications
- Reduce delay in medication administration
- Medication education

Be competent and proactive!
Targeted Temperature Management in Post Cardiac Arrest Patients

Questions: treesa.joseph@atlantichealth.org

Treesa Joseph, PharmD
PGY-1 Pharmacy Resident
Atlantic Health System

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