Therapeutic Hypothermia:

A pharmacist’s guide to being cool

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MICU Pharmacotherapy Specialist

Objectives

- Evaluate the evidence supporting therapeutic hypothermia.
- Identify the appropriate patient for therapeutic hypothermia.
- Discuss how to manage a patient during therapeutic hypothermia.

Cardiac Arrest

- Out-of-Hospital
  - Approximately 380,000 patients/year
  - Overall survival 5 – 8%
  - Surviving pts 50% with neurological defects
- In-Hospital
  - Approximately 210,000 patients/year
  - Survival rate 23%

GOALS OF POSTRESUSCITATION

- Optimize cardiopulmonary function and systemic perfusion
- Transport out of hospital arrest to hospital
- Identify precipitating causes
- Institute measures to prevent recurrence
- Institute measures that may improve long-term, neurological intact survival

Post Cardiac Arrest Brain Injury

- Common cause of morbidity/mortality
- Clinical manifestations vary
  - Coma to brain death
- Time = Brain function

Cardiac Arrest

Ischemia

Reperfusion

Inflammatory Cascades

Mitochondrial dysfunction

Oxygen-free Radicals

Hypothermia

Excitotoxicity

Inflammation

Cell Death

Cerebral Edema

Hypothermia Neuroprotection

- Decrease cerebral metabolism
- Decreases glutamate
- Reduces intracellular acidosis
- Decreases inflammatory response
- Stabilization of neuronal cell membranes
- And much more…

Hypothermia Definition

<table>
<thead>
<tr>
<th>Temperature Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 – 37.4 C</td>
<td>Normothermic</td>
</tr>
<tr>
<td>34 – 35.9 C</td>
<td>Mild therapeutic hypothermia</td>
</tr>
<tr>
<td>32 – 33.9 C</td>
<td>Moderate therapeutic hypothermia</td>
</tr>
<tr>
<td>30 – 31.9 C</td>
<td>Moderate/Deep therapeutic hypothermia</td>
</tr>
<tr>
<td>&lt; 30 C</td>
<td>Deep therapeutic hypothermia</td>
</tr>
</tbody>
</table>

Hypothermia Definition

- 36 – 37.4 C Normothermic
- 34 – 35.9 C Mild therapeutic hypothermia
- 32 – 33.9 C Moderate therapeutic hypothermia
- 30 – 31.9 C Moderate/Deep therapeutic hypothermia
- < 30 C Deep therapeutic hypothermia

History of Hypothermia

- 1803: Cold Russian’s
- 1812: Saving limbs
- 1937: Preventing cancer
- 1953: Dogs and monkeys – saved
- 1959: Widely used in surgery
- 1960’s – 1990’s: complications arise
- 2002: It’s cool to be cool… again

Bernard et al.

- Randomized, controlled trial
  - Neurological assessment NOT blinded
- Inclusion: Vfib out of hospital arrest
- 77 patients included
  - 43 hypothermia – 34 normothermia
- Hypothermia:
  - 33 C x 12 hours; rewarmed over 6 hours

Neurological Outcome

<table>
<thead>
<tr>
<th>Pittsburgh Cerebral Performance Category Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC 1</td>
</tr>
<tr>
<td>CPC 2</td>
</tr>
<tr>
<td>CPC 3</td>
</tr>
<tr>
<td>CPC 4</td>
</tr>
<tr>
<td>CPC 5</td>
</tr>
</tbody>
</table>

Baseline Characteristics

- Characteristics well matched
- Average time to ROSC: 26 min
Complications

- Not clinically significant adverse effects
  - Bradycardia
  - Decrease in SVR
  - Increase of potassium during rewarming
  - Hyperglycemia
  - No difference in WBC/Platelet

Neurological Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothermia n = 43</th>
<th>Normothermia n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/Minimal Disability</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>Moderate Disability</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Severe Disability (Awake)</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Severe Disability (Unconscious)</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Death</td>
<td>22%</td>
<td>23%</td>
</tr>
</tbody>
</table>

HACA Study Group

- Randomized, controlled trial
  - Neurological assessment blinded to treatment
- Inclusion: Vfib/Vtach out of hospital
- 275 patients included
  - 137 hypothermia – 138 normothermia
- Hypothermia:
  - 32 - 34 C x 24 hours; rewarmed over 8 hours

Baseline Characteristics

- Characteristics well matched
- Average time to ROSC: 22 min

Complications

- No clinically/statistically significant difference in adverse effects
- Trend toward increase in sepsis
  - Not statistically significant

Absolute Survival
Neurological Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothermia n = 137</th>
<th>Normothermia n = 138</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable Neurological Outcome</td>
<td>55%</td>
<td>39%</td>
<td>0.009</td>
</tr>
<tr>
<td>Death</td>
<td>41%</td>
<td>55%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Guideline Recommendations

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32 – 34°C for 12 – 24 hours when the initial rhythm was ventricular fibrillation

- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Implementation Study

- Retrospective study
- Inclusion: Out of hospital cardiac arrest
- 109 patients included
  - 55 hypothermia
  - 54 normothermia
- Hypothermia:
  - 33°C x 24 hours; passive rewarming

Outcomes – Vfib

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothermia n = 43</th>
<th>Normothermia n = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/Minimal Disability</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Moderate Disability</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Severe Disability (Awake)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Severe Disability (Unconscious)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Death</td>
<td>17</td>
<td>24</td>
</tr>
</tbody>
</table>

Outcomes – Asystole/PEA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hypothermia n = 12</th>
<th>Normothermia n = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/Minimal Disability</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Moderate Disability</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe Disability (Awake)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Severe Disability (Unconscious)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Registry Data

- Data prospectively collected
- Inclusion: Out of hospital cardiac arrest
- 1145 patients included
- Hypothermia
  - 32 – 34 C x 24 hours

Neurological Outcome

708 pts
Vfib/Vtach

<table>
<thead>
<tr>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=457</td>
<td>n=251</td>
</tr>
<tr>
<td>Good Outcome n=201</td>
<td>Good Outcome n=73</td>
</tr>
<tr>
<td>44%</td>
<td>29%</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Neurological Outcome

438 pts
Asystole/PEA

<table>
<thead>
<tr>
<th>Hypothermia</th>
<th>Normothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=261</td>
<td>n=176</td>
</tr>
<tr>
<td>Good Outcome n=38</td>
<td>Good Outcome n=30</td>
</tr>
<tr>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>p=0.48</td>
<td></td>
</tr>
</tbody>
</table>

In-Hospital Cardiac Arrest

- In hospital etiology differ
- “Code” team readily available
- National Registry of CPR
  - 36,902 inpatients with cardiac arrest
  - Survival 18%
- Recommended if neurological injury suspected

Who do you cool?

- Cardiac arrest due to Vfib/Vtach
- Return of spontaneous circulation 60 min
- Coma (not following commands)
- Treatment initiated within 6 hrs of arrest
**Who do you NOT cool?**

- Hemorrhagic stroke
- Cardiac arrest due to trauma
- Glasgow Coma Scale > 8
- Uncontrolled active bleeding
- Uncontrolled arrhythmias
- Terminal Illness/DNR CCO
- Baseline comatose/impaired cognitive fnx

**Questionable Patients**

- PEA arrest
- Inpatient cardiac arrest
- Cardiac arrest > 60 minutes
- Baseline coagulopathy
- Severe hypotension
- Systemic infection
- Pregnancy

**Therapeutic Hypothermia Phases**

- Induction
  - Instability phase
- Maintenance
  - Prevention of long term side effects
- Rewarming
  - Prevention of side effect

**Management of Phases**

- Cooling Methods - External
  - Ice packs, wet linens, fans
  - Cooling blankets: Bair Hugger
  - Pre-refrigerated cooling pads
  - Cold water immersion
  - Hydrogel-coated pads: Arctic Sun

**Arctic Sun**

[Image of Arctic Sun device]
Cooling Methods - Internal

- Infusion of ice cold fluids (4°C)
- Intravascular devices

Monitoring Temperature

- Core temp needs to be monitored
- Gold standard: Pulmonary artery catheter
- Multiple other sites:
  - Bladder
  - Rectum
  - Esophagus

Side Effects of Hypothermia

- Begins at 35.5°C
- Negative effects:
  - Increased metabolism/O2 consumption
  - Heat generation
- Ceases at 33 – 34°C
- Identification can be problematic
  - Seizures vs. Shivering

Management of Shivering

- Opiates
  - Meperidine
- Benzodiazepines
- Propofol
- Paralytic agents
  - Clonidine
  - Dexmedetomidine
  - Tramadol
  - Buspirone
  - Magnesium
  - Warm air skin counter warming

- Propofol drip – up to 50mcg/kg/min
- Fentanyl drip – up to 200mcg/hr
- Rocuronium 50mg IVP q2hr prn shivering

- Titrate medications:
  - Visible shivering
  - Decrease water temperature
  - Upward arrows
Cardiovascular Effects

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 – 36</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>≤ 35</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>≤ 34</td>
<td>Increase in BP, CVP, SVR</td>
</tr>
<tr>
<td>≤ 32</td>
<td>Mild arrhythmias</td>
</tr>
<tr>
<td>&lt; 28</td>
<td>High risk of tachyarrhythmias</td>
</tr>
</tbody>
</table>

Electrolyte disorders

- Frequent during induction phase
- 2 mechanisms:
  - Increased renal excretion
  - Intracellular shifts
- Diligent monitoring
- Replace appropriately
  - Aggressive during induction
  - Judicious during rewarming

Electrolyte disorders

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Hyperglycemia

- Decreased insulin sensitivity
- Reduced insulin secretion
- Treatment typically with insulin drip
- Problematic with rewarming
  - Hypoglycemia

Gastrointestinal

- Impaired bowel function/ileus
  - NPO until rewarmed
- Increase in amylase
  - Common, but insignificant
- Increase in LFTs

Impaired Coagulation

- Clinically significant bleeding is limited
- < 35 C: platelet function decreased
- < 33 C: clotting factors affected
- Mild hypothermia (35 C) may be considered in high risk patients

Infection

- Impaired immune function
- Inhibits inflammatory response
- If > 24 hours, increase risk
- Hard to monitor temperature curve
- Culture prior to initiation of hypothermia
- Empiric antibiotics?
Drug Clearance

- Reduction of liver enzymes
- Reduced liver perfusion
- Decrease excretion
- Increased drug levels
- Enhanced drug effects


Drug Clearance

- Fentanyl, morphine
- Propofol
- Midazolam
- Rocuronium
- Nitrates
- Phenytoin
- Titrate to effect
- Clinically, no dose adjustment needed
- Intermittent dosing


What if they wake up?

STOP!!!!

After patient is rewarmed...

- Discontinue all sedation and paralytics rapidly
- Assess neurological function
  - Head CT/EEG
- Consult neurology

Conclusions

- Therapeutic hypothermia has significant improved survival and outcomes
- Appropriate patient population is key
- Management of side effects is essential
- Future implications are endless

Future/Current Implications

- Stroke
- Spinal Cord Injury
- TBI
- Neonatal Hypoxia