Feasibility of Therapeutic Hypothermia in Ischemic Stroke

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The therapeutic target

- Achieving biologically significant lowering of temperature in the ischemic penumbra
- Rapid enough
- Long enough
The therapeutic target

- Achieving biologically significant lowering of temperature in the ischemic penumbra
- Rapid enough
- Long enough
- Selective
Temperatures (mean of patients' means shown) (°C) of ischemic and normal-appearing brain at admission to hospital and follow-up at around 5 days after stroke. CNL, contralateral normal brain; CSI, chemical shift imaging; DAL, definitely abnormal tissue; INL, ipsilateral normal brain; PAL, possible abnormal tissue; PAL+, tissue one voxel thick immediately outside the lesion.
Challenges

- Central thermoregulation
- Peripheral thermoregulation
- Compartimentalization
- Effective and timely cooling
- Shivering
- Adverse effects
- Drugs
Central Thermoregulation

- Hypothalamic control of body temperature set point
- Variations
  - Circadian
  - Fever
  - Hypothermia
- Shivering threshold
- Feedback mechanisms
  - Warm feet, hands, head
  - Ethanol
Peripheral thermoregulation

- Vasodilation/constriction
- Skin sympathetic innervation
- Voluntary muscle activity
- Shivering
- Centralization of circulation
Cooling in time

- Fluids
- Intravascular
- Surface
Coolaid Øresund

Ovesen et al, Acta Neurol Scand 2013
Maintaining Cooling over time

Modulation of central and peripheral thermoregulation:

- Anti-shivering drugs
- Feedback
  - Mittens
  - Socks
  - Bear hugger
Surface Cooling Device with Cooling Pads

Piironen et al., Nordic Stroke 2013
Dexmedetomidine, Meperidine and Buspirone

- Dexmedetomidine is a selective alpha2-adrenoreceptor agonist that lowers the shivering threshold by 0.7°C

- Dexmedetomidine is sedative and analgesic, but does not depress the respiratory drive

- Meperidine lowers the shivering threshold by 1.1°C and additively with dexmedetomidine by 1.9°C

- Buspirone reduces the shivering threshold 0.7°C and synergistically with meperidine by 2.3°C
### Mild hypothermia after IV thrombolysis

- **15/18 patients** spent 12 hours at <36°C
- **16/18 patients** reached <35.5°C

<table>
<thead>
<tr>
<th>Time Description</th>
<th>Hours (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from symptom onset to hypothermia induction</td>
<td>6.0 (4.5-6.5)</td>
</tr>
<tr>
<td>Time from hypothermia induction to &lt;35.5°C</td>
<td>4.5 (3-11)</td>
</tr>
<tr>
<td>Time &lt;35.5°C</td>
<td>10.5 (1-17)</td>
</tr>
<tr>
<td>Time &lt;36°C</td>
<td>16.8 (3-21)</td>
</tr>
<tr>
<td>Time of rewarming</td>
<td>7 (2-9)</td>
</tr>
<tr>
<td>Total time from induction to normothermia</td>
<td>23 (15-29)</td>
</tr>
</tbody>
</table>
Comparing hypothermia patients of ICTuS-L and Oresund COOLAID trial

<table>
<thead>
<tr>
<th></th>
<th>ICTuS-L</th>
<th>Oresund COOLAID</th>
<th>Our Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS baseline</td>
<td>14.3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>NIHSS 3-months</td>
<td>6.3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>mRS 3-months</td>
<td>-</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>mRS 0-1 3-months</td>
<td>18%</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>Pneumonia rate</td>
<td>50%</td>
<td>35%</td>
<td>39%</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>21%</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Conclusion

Rapid induction
Close clinical monitoring
Early treatment with anti-shivering drugs
Physical anti-shivering strategies
Individualized temperature target
multicentre clinical trial

1:1 randomization

therapeutic cooling vs standard stroke treatment

1500 patients with acute ischaemic stroke

masked outcome assessment
Historical background

- B. Hindfelt 1976 Acta Neurologica Scandinavica

"The prognostic significance of subfebrility and fever in ischaemic cerebral infarction"

110 patients
retrospective
Temperatures (mean of patients' means shown) (°C) of ischemic and normal-appearing brain at admission to hospital and follow-up at around 5 days after stroke. CNL, contralateral normal brain; CSI, chemical shift imaging; DAL, definitely abnormal tissue; INL, ipsilateral normal brain; PAL, possible abnormal tissue; PAL+, tissue one voxel thick immediately outside the lesion.
Clinical trials

- Schwab et al. 1998 Stroke
  - 25 patients with severe ischemic stroke in the MCA territory
  - external cooling to 33°C, 14±7 h after stroke
  - duration of cooling 48 – 72 h
  - 14 patients survived: 56% compared to 20%
  - pneumonia in 10 of 25 patients
  - herniation after rewarming main cause of death
Clinical trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>After Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP, mm Hg</td>
<td>20.9±12.4</td>
<td>13.4±8.3*</td>
<td>19.4±8.7</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>68±14</td>
<td>78±21*</td>
<td>70±21</td>
</tr>
<tr>
<td>Brain temperature, °C</td>
<td>38.4±1.3</td>
<td>33.3±0.7</td>
<td>37.4±0.9</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>37.5±0.9</td>
<td>33.0±0.2</td>
<td>36.8±0.9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84±6</td>
<td>62±10*</td>
<td>80±12</td>
</tr>
</tbody>
</table>
Clinical trials

- COOL AID (1) Krieger et al. 2001 Stroke
  - 10 patients with NIHSS 20 treated with trombolysis
  - external cooling to 32 °C, 6.2 ± 1.3 h after stroke
  - duration of cooling 47 ± 20 h

- 7 patients survived with Rankin 3.1 ± 2 at 3 months
Clinical trials

- COOL AID (1) Krieger et al. 2001 Stroke
  - non-critical complications
    - bradycardia
    - hypotension
    - pneumonia
  - critical complications
    - rapid AF
    - herniation (1 hemorrhagic)
COOLAID Øresund

Stroke onset

Initial stroke treatment

Good treatment response

Standard stroke treatment In stroke department

Control

Randomization

Endovascular cooling in Danish centre

Surface cooling in Swedish centre

No treatment response

Ovesen et al, Acta Neurol Scand 2013
Method

• General intensive care unit (ICU)

• Sedation with propofol and paralyzed with rocuronium

• Therapeutic hypothermia for 24 hours followed by controlled rewarming

Ovesen et al, Acta Neurol Scand 2013
Cooling Modalities

Endovascular cooling (Danish site):
• Endovascular cooling catheter in the vena cava (Thermogard XP®)

Surface cooling (Swedish site):
• Surface cooling pads (Arctic Sun®)

Ovesen et al, Acta Neurol Scand 2013
Cooling Induction Time

Ovesen et al, Acta Neurol Scand 2013
Pneumonia

Concurrent risk factors:

- Stroke
- Mechanical ventilation
- Cooling treatment

Ovesen et al, Acta Neurol Scand 2013
multicentre clinical trial

1:1 randomization

therapeutic cooling vs standard stroke treatment

1500 patients with acute ischaemic stroke

masked outcome assessment
Consortium

EC: Kollmar R, Krieger D, McLeod M, Petersson J, Schwab S, Szabo I, vDWorp HB,
Treatment

Cooling initiated < 6 hours of symptom onset with an intravenous infusion of 20 ml/kg cooled normal saline (4°C) over 30 to 60 minutes, followed by either surface or endovascular cooling to 34 to 35°C for 24 h

Controlled rewarming 0.3°C/h

Shivering and discomfort will be prevented and treated with anti-shivering drugs: meperidine and buspirone

1st patient randomized November 2013
Hemorrhage Insult

- ■ Hemorrhage + saline control
- ○ Hemorrhage + HPI-201
- ▲ Hemorrhage + HPI-201 at normothermia

Temperature (°C)

HPI-201 (2 mg/kg)

HPI-201 (1 mg/kg)

Time (min)

Wei et al 2013 Neuroscience
Further developments

- target reperfusion injury after revascularization
- adjunctive to other neuroprotective strategies
- focal cooling
- 33 vs 34 °C
- 9 h vs 72 h
- very early vs delayed start – pre-hospital cooling
- surface vs intravascular
Conclusion

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Close clinical monitoring
Early treatment with anti-shivering drugs
Physical anti-shivering strategies
Individualized temperature target
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Hypothermia (n=18)</th>
<th>Control (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shivering</td>
<td>11 (61)</td>
<td>1 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7 (39)</td>
<td>2 (11)</td>
<td>0.054</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>12 (71)</td>
<td>7 (39)</td>
<td>0.060</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>2 (11)</td>
<td>0.157</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (5.9)</td>
<td>4 (22)</td>
<td>0.167</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (33)</td>
<td>2 (11)</td>
<td>0.089</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (38)</td>
<td>2 (22)</td>
<td>0.109</td>
</tr>
<tr>
<td>FA during hypothermia</td>
<td>3 (17)</td>
<td>3 (17)</td>
<td>0.939</td>
</tr>
<tr>
<td>AMI</td>
<td>1 (6)</td>
<td>0</td>
<td>0.310</td>
</tr>
<tr>
<td>Renal decompensation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Brain CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain edema</td>
<td>5 (28)</td>
<td>8 (44)</td>
<td>0.298</td>
</tr>
<tr>
<td>Parenchymal hemorrhage (all)</td>
<td>6 (33)</td>
<td>5 (28)</td>
<td>0.717</td>
</tr>
<tr>
<td>Craniectomy</td>
<td>0</td>
<td>1 (6)</td>
<td>0.310</td>
</tr>
<tr>
<td>Electrolyte disturbance</td>
<td></td>
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<tr>
<td>Hypomagnesemia</td>
<td>10 (53)</td>
<td>2 (13)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (22)</td>
<td>3 (17)</td>
<td>0.423</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6 (33)</td>
<td>1 (6)</td>
<td>0.035</td>
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<tr>
<td>CK increase</td>
<td>3 (17)</td>
<td>4 (22)</td>
<td>0.674</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5 (29)</td>
<td>6 (33)</td>
<td>0.803</td>
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<tr>
<td>Results of blood gas analysis</td>
<td></td>
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<tr>
<td>Hypoxemia</td>
<td>8 (50)</td>
<td>1 (9)</td>
<td>0.004</td>
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<tr>
<td>Hypercapnia</td>
<td>7 (44)</td>
<td>0</td>
<td>0.002</td>
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<tr>
<td>Acidosis</td>
<td>5 (31)</td>
<td>0</td>
<td>0.016</td>
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<tr>
<td>Alkalosis</td>
<td>2 (13)</td>
<td>4 (24)</td>
<td>0.371</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AMI, acute myocardial infarction; CT, computed tomography; CK creatinin kinase. All values are n (%).