Current status of temperature management in the neuro-ICU

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Neurologic Intensiv Care Unit Innsbruck, Austria
Gregor Brössner has received an unrestricted Grant by Alsius Corp\textsuperscript{®}.. Speakers honoraria and travel grants from Zoll\textsuperscript{®} Corp. and Euromed.
Outline:

Pathophysiological effects of fever
Mechanisms of therapeutic hypothermia
Practical aspects of hypothermia
Concept of prophylactic normothermia

Ongoing trials / future indications of temperature management

Discussion

40 minutes
**Impact of Fever on Outcome in Patients With Stroke and Neurologic Injury: A Comprehensive Meta-Analysis**

David M. Greer, Susan E. Funk, Nancy L. Reaven, Myrsini Ouzounelli and Gwen C. Uman

Metaanalysis of 39 studies and 14,000 patients

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>No. of Articles/Hypotheses*</th>
<th>RR</th>
<th>Fever/Higher Body Temperature Associated Significantly With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>24/24</td>
<td>1.5</td>
<td>Death</td>
</tr>
<tr>
<td>GOS</td>
<td>9/11</td>
<td>1.3</td>
<td>Neurological deficit/death</td>
</tr>
<tr>
<td>BI</td>
<td>8/10</td>
<td>1.9</td>
<td>More dependence</td>
</tr>
<tr>
<td>mRS</td>
<td>5/5</td>
<td>2.2</td>
<td>Lower functioning</td>
</tr>
<tr>
<td>CSS</td>
<td>5/8</td>
<td>1.4</td>
<td>Greater severity</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>6/6</td>
<td>2.8</td>
<td>Longer ICU stay</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>3/3</td>
<td>3.2</td>
<td>Longer hospital stay</td>
</tr>
</tbody>
</table>
Negative effects of fever, „secondary neuronal injury“ II:
Mechanisms of temperature management:

*Primary injury:*
- Traumatic brain injury (TBI)
- Stroke
- Hypoxia
- Intracerebral hematoma
- Metabolic

ICP = intracranial pressure
Mechanisms of temperature management:

**Primary Injury:**
- Traumatic brain injury (TBI)
- Stroke
- Hypoxia
- Intracerebral hematoma
- Metabolic

**Secondary Injury:**
- Brain edema
- Stroke (vasospasm)
- Electrolyte disturbance (Ca, Na/K)
- Neuro-excitation (seizures)

ICP = Intracranial pressure
Mechanisms of temperature management:

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elevation of ICP
Mechanisms of temperature management:

**Primary Injury:**
- Traumatic brain injury (TBI)
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**Normo-/Hypothermia**

ICP = intracranial pressure
Pathophysiologische mechanism induced by isch. Stroke:

- Arterial Occlusion
  - CBF-reduction
  - metabolic deficit
    - Release of glutamate
    - dysbalance of elect.
      - Influx of Ca$^{2+}$
      - Free radicals
        - Membrane dysfunction
    - Reperfusion
      - BBB-dysfunction
      - Inflammation
      - Edema
      - Necrosis
      - Apoptosis
Neuroprotection after Stroke:

Arterial occlusion

CBF-Reduction

Metabolic defizit

Reperfusion

t-PA

BBB- dysfunction

Inflammation

MMP-Inhib.

Edema

Nerosis

Apoptosis

NMDA-Antag.

Influx of Ca^{2+}

Calcium-Antag.

GABA-Antag.

Inflammation

Membrane dysfunction

Free radicals

Glutamate-Antag.

Release of glutamate

Neutrophil-Antag.

GCSF/EPO
Onsets of Hypothermia:

- Hypothermia
- Fever

Arterial occlusion
- CBF-reduction
- Metabolic deficit

Reperfusion
- BBB dysfunction

Inflammation

Edema

Release of glutamate

Influx of Ca^{2+}

Free radical

Membrane dysfunction

Dysbalance of elect.

Necrosis

Apoptosis
(Possible) indications for therapeutic hypothermia:

Comatose survivors after cardiac arrest (refractory)
Elevated intracranial pressure (ICP)
Asphyctic neonates
Hepatic encephalopathy
Heat stroke

Stroke
Traumatic brain injury
Myocardial infarction
Spinal cord injury
Status epilepticus
Meningitis
Phases of hypothermia:

- Induction
- Maintenance
- Rewarming
Practical approach to hypothermia:

**Pre-Induction:**
avoid shivering through medication and counter warming

**Induction:**
as fast as possible (ice cold saline 4°C i.v., 30ml/kg /bw)
Target temperature 34° - 35°C (avoid overshoot)

**Maintenance:**
at least 24hrs (up to 7 days)
closely maintain target temperature (use devices – endovascular vs surface)

**Rewarming:**
very slow (!)
controlled rewarming (0.1 °C/hr)

**Post rewarming:**
avoid fever (close temperature surveillance)
Therapeutic temperature management requires:

**continuous monitoring of:**

- body core temperature
- cardiovascular functions
- renal functions

**standardized**

- surveillance of infections
- laboratory work up
- treatment of shivering

ICP monitoring
Limitations of Hypothermia:

Lack of Effect of Induction of Hypothermia After Acute Brain Injury

Guy L. Clifton, M.D., Emmy R. Miller, Ph.D., R.N., Sung C. Choi, Ph.D., Harvey S. Levin, Ph.D., Stephen McCauley, Ph.D., Kenneth R. Smith, Jr., M.D., J. Paul Muizelaar, M.D., Ph.D., Franklin C. Wagner, Jr., M.D., Donald W. Marion, M.D., Thomas G. Luerssen, M.D., Randall M. Chesnut, M.D., and Michael Schwartz, M.D.

NEJM, 2001

Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial


Lancet Neurology, 2010
Limitations – Infections:

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L): Final Results

Table 3. Outcome Measures Between HY and NT Patients

<table>
<thead>
<tr>
<th></th>
<th>HY (Groups 2, 5, 6; n=28)</th>
<th>NT (Groups 1, 3, 4; n=30)</th>
<th>Fisher Exact Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–1 at 90 days</td>
<td>5</td>
<td>7</td>
<td>0.747</td>
</tr>
<tr>
<td>NIHSS at 90 day (mean±SD)</td>
<td>6.3 (±6.6)</td>
<td>3.8 (±3.0)</td>
<td>0.355</td>
</tr>
<tr>
<td>At least one SAE (%)</td>
<td>75</td>
<td>43.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>50</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>All ICH (%)</td>
<td>28.6</td>
<td>20</td>
<td>0.752</td>
</tr>
<tr>
<td>Symptomatic ICH (%)</td>
<td>3.6</td>
<td>10</td>
<td>0.609</td>
</tr>
<tr>
<td>Mortality by 90 days (%)</td>
<td>21.4%</td>
<td>16.7</td>
<td>0.744</td>
</tr>
</tbody>
</table>

SAE indicates serious adverse event; ICH, intracerebral hemorrhage.

Hemmen et al., Stroke 2010
Controlled prophylactic normothermia
Concept of controlled prophylactic normothermia:

**Negative effects of fever:**

- independent predictor of unfavorable outcome
- breakdown of blood-brain-barrier
- vascular permeability ↑
- leads to brain edema
- mitochondrial dysfunction
- increased metabolic demand ↑
- free radicals ↑
- focal hyperthermia
- „Thermopooling“ ↑
- Reperfusion Injury ↑

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- free radicals↑
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- Reperfusion Injury ↑

**Negative effects of hypothermia:**
- Hypotonia (TBI)
- Infectious complications
- Magnesium
- Sodium
- Shivering
- **Rewarming Injury** („rebound effect“)
- „awake patient“
- reduction of rTPA action (?)

Concept of controlled prophylactic normothermia:

**Negative effects of fever:**
- independent predictor of unfavorable outcome
- breakdown of blood-brain barrier
- free radicals ↑
- focal hyperthermia
- „Thermopooling“↑
- Reperfusion Injury ↑

**Negative effects of hypothermia:**
- Hypotonia (TBI)

**controlled normothermia (36.5°C)**
- avoidance of the NEGATIVE effects of fever
- „awake patient“
- reduction of rTPA action (?)

Cerebrovascular diseases – Normothermia I

Prophylactic, Endovascularly Based, Long-Term Normothermia in ICU Patients With Severe Cerebrovascular Disease: Bicenter Prospective, Randomized Trial
Gregor Broessner, Ronny Beer, Peter Lackner, Raimund Helbok, Marlene Fischer, Bettina Pfausler, Janelle Rhorer, Lea Küppers-Tiedt, Dietmar Schneider and Erich Schmutzhard

36,5°C

CoolGard 3000, Zoll Corp.

Temp > 37,9°C

Conventional temperature management treatment, stepwise escalating

1. Paracetamol 500mg p.o.
2. Naproxen 500mg p.o.
3. Pethidin 100mg i.v.
4. ICE packs
5. Cool „washing“
6. Cooling blankets (Blanketrol®)

Broessner et. al., Stroke 2009

SAH HH 3-5
ICH GCS ≤ 10
Stroke NiHSS ≥ 15

conventional „controls“
### Cerebrovascular diseases – Normothermia II

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>CoolGard (n=51)</th>
<th>Control (n=51)</th>
<th>P Value</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>4 (8)</td>
<td>6 (12)</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>19 (37)</td>
<td>22 (43)</td>
<td></td>
<td>168 hrs</td>
<td></td>
</tr>
<tr>
<td>SAH</td>
<td>28 (55)</td>
<td>23 (45)</td>
<td></td>
<td>336 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Broessner et. al., Stroke 2009
Primary Outcome

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Total Fever Burden in Hours (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CoolGard (n=51)</td>
</tr>
<tr>
<td>Overall</td>
<td>51</td>
</tr>
<tr>
<td>No.</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.5±3.3</td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Broessler et. al., Stroke 2009*
## Sekondary Outcome (AE)

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Through Neuro-ICU Discharge</th>
<th>Through Day 30</th>
<th>Through Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CoolGard n (%)</td>
<td>Control n (%)</td>
<td>P Value</td>
</tr>
<tr>
<td>Overall</td>
<td>48 (94)</td>
<td>43 (84)</td>
<td>0.20</td>
</tr>
<tr>
<td>Infectious</td>
<td>48 (94)</td>
<td>40 (78)</td>
<td>0.04</td>
</tr>
<tr>
<td>Noninfectious</td>
<td>19 (37)</td>
<td>20 (39)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Broessner et. al., Stroke 2009
# Tertiary Outcome

## Table 5. Neurologic Function

<table>
<thead>
<tr>
<th></th>
<th>CoolGard n (%)</th>
<th>Control n (%)</th>
<th>CoolGard n (%)</th>
<th>Control n (%)</th>
<th>CoolGard n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discharge</td>
<td>Day 30</td>
<td>Month 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>9 (18)</td>
<td>12 (24)</td>
<td>18 (35)</td>
<td>14 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td>6 (12)</td>
<td>3 (6)</td>
<td>0</td>
<td>3 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>25 (49)</td>
<td>21 (41)</td>
<td>9 (18)</td>
<td>9 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>8 (16)</td>
<td>7 (14)</td>
<td>8 (16)</td>
<td>9 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good recovery</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>9 (18)</td>
<td>12 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubated</td>
<td>0</td>
<td>3 (6)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>2 (4)</td>
<td>7 (14)</td>
<td>4 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.81</td>
<td>0.55</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Broessner et. al., Stroke 2009*
Rate of infectious complications vs. inflammatory parameters?

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>CoolGard (n=51)</th>
<th>Control (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal data of inflammatory parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/100 mL (mean±SD)</td>
<td>10.8±6.0</td>
<td>8.6±5.6</td>
<td>0.03</td>
</tr>
<tr>
<td>WBCs, G cells/L (mean±SD)</td>
<td>10.3±3.3</td>
<td>10.5±2.8</td>
<td>0.84</td>
</tr>
<tr>
<td>IL-10, pg/mL (mean±SD)</td>
<td>11.3±17.2</td>
<td>10.9±16.5</td>
<td>0.72</td>
</tr>
<tr>
<td>IL-6, pg/mL (mean±SD)</td>
<td>95.2±82.2</td>
<td>72.7±83.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Procalcitonin, µg/L (mean±SD)</td>
<td>0.4±1.1</td>
<td>0.7±1.4</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Broessner & Schmutzhard et al., Stroke 2010.
Cerebrovascular diseases – Normothermie V

Figure C: CRP level over days for Control and Device groups.

Figure D: CRP level over days for NSAID and No NSAID patients.

Broessner & Schmutzhard et al., Stroke 2010
Table 2. Predictors of Unfavorable Neurologic Long-Term Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.09</td>
<td>1.04 - 1.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endovascular group</td>
<td>Reference Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1.56</td>
<td>0.5 - 4.88</td>
<td>0.44</td>
</tr>
<tr>
<td>No NSAID</td>
<td>Reference Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID applied</td>
<td>0.36</td>
<td>0.1 - 1.24</td>
<td>0.1</td>
</tr>
<tr>
<td>LOS neuro-ICU</td>
<td>1.01</td>
<td>0.99 - 1.04</td>
<td>0.35</td>
</tr>
<tr>
<td>Sex</td>
<td>0.58</td>
<td>0.2 - 1.68</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Normothermia and TBI I:

Induced Normothermia Attenuates Intracranial Hypertension and Reduces Fever Burden after Severe Traumatic Brain Injury

severe TBI GCS ≤ 8

N= 21 patients
endovaskular normothermia (TT 36 – 36,5°C) 
(Zoll®, Coolgard®) over 36 hrs

comparison with „historic controls“ (N=21)

ICP monitoring (Licox®)

Puccio et al., Neuro Crit Care 2009
Normothermia and TBI il:

![Box plot showing comparison between control and induced normothermia in mean ICP (mmHg). The Wilcoxon Signed Ranks Test p-value is 0.027.]
Normothermia and TBI il:
Therapeutic hypothermia
Can prophylactic endovascular normo-/hypothermia influence brain temperature (in patients with severe TBI)?

Inclusion criteria:

severe TBI (intial GCS ≤ 8)

Interventions:

ICP + temperature probe (Neurovent-Temp-P, Raumedic AG, Muenchberg, Germany)
endovascular normo/ hypothermia (CoolGard 3000®, Zoll®)

N=7 patients

Fischer & Broessner et al., Neurosurgery 2011
TBI – brain versus bladdertemperature under normo/hypothermia

CC \( r = 95 \)

Brain Temperature

Urinary Bladder Temperature

Fischer & Broessner et al., Neurosurgery 2011
Hypothermia and ICH:
Hypothermia and ICH:
Hypothermia and ICH:
Hypothermia in ICH rat model:

The effects of selective brain hypothermia on intracerebral hemorrhage in rats

Matthew Fingas\textsuperscript{a}, Darren L. Clark\textsuperscript{a}, Frederick Colbourne\textsuperscript{a,b,*}
Hypothermia in ICH rat model:
Hypothermia and ICH:

Hypothermia Reduces Perihemorrhagic Edema After Intracerebral Hemorrhage

Rainer Kollmar, Dimitre Staykov, Arnd Dörrler, Peter D. Schellinger, Stefan Schwab and Jürgen Bardutzky

Normo / Hypothermia over 10 days

<table>
<thead>
<tr>
<th>Hypothermia (n=12)</th>
<th>Control (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Brain scans" /></td>
<td><img src="image2.png" alt="Brain scans" /></td>
</tr>
</tbody>
</table>
Hypothermia and ICH:

Kollmar, Staykov et al., Stroke 2010
Ongoing trials with temperature management

**Clinicaltrials.gov** (National Institutes of Health (NIH))

**Hypothermia:**

78 registered trials (recruiting or before recruiting)

*Indications: Stroke, bact. meningitis, status epilepticus, TBI, SAH, cardiac arrest, asphyxia a.m.m.*

**Controlled normothermia:**

9 registered trials (recruiting or before recruiting)
Ongoing trials with temperature management:

Cooling in intracerebral hemorrhage (CINCH) trial: protocol of a randomized German–Austrian clinical trial

Rainer Kollmar¹*, Eric Juettler², Hagen B. Huttnér¹, Arnd Dörfler³, Dimitre Staykov¹, Bernd Kallmuenzer¹, Erich Schmutzhard⁴, Stefan Schwab¹, Gregor Broessner⁴ for the CINCH investigators
Ongoing trials with temperature management:

ICTuS-2/3

Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke-2/3
Ongoing trials with temperature management:

EXTENDED SYNPOSIS

EuroHYP-1: A European, multicentre, randomised, phase III, clinical trial of hypothermia plus medical treatment versus best medical treatment alone for acute ischaemic stroke
Summary I:

*fever* has to be *avoided in patients with acute neuronal injury* by any means.

**Good evidence for hypothermia (RCT):**

- Post resuscitation
- Refractory elevated ICP
- Asphyctic neonates

Promising results in Stroke, ICH....

*(longterm-)* pro*phylactic endovasacular normothermia* is *efficacious* and *feasible*
Summary II:

**Understanding** and **treating the limitations** in therapeutic temperature management is pivotal:

(even under prophylactic normothermia) close and **standardized surveillance** for **infections** is absolutely mandatory – treatment of fever does **not replace treatment of infections**

use anti-shivering protocol

avoid fever rebound
Сердечное спасибо!