Neurotrauma: The Place for Cooling

▶ Cooling: to achieve hypothermia
  ▶ History, evidence, open questions

▶ Cooling: to achieve normothermia
  ▶ Evidence, open questions

▶ Cooling: Practical Aspects
Hypothermia: History

» Hypothermia for neuroprotection mentioned in Greek medical texts (acc. to Maas AIR & al., Chapter 20, Head Injury, Hodder Arnold, London, UK 2005)

» 1945 – 1975: widely used (on wards!)
  » “generalized refrigeration” (T. Fay)
  » “artificial hibernation” (w. phenothiazines)

» 1975 – 1990: use discontinued due to management problems
Facts about Hypothermia

Hypothermia: beneficial metabolic effects

- Reduces CBF by 5% / °C reduction of BT
- Reduces CMRO$_2$ and avDO$_2$
- Increases tissue ATP concentration

Improves mismatch between blood flow and metabolism
Facts about Hypothermia

Hypothermia: other beneficial effects
- Reduces inflammatory response
- Reduces neurotransmitter turnover

Hypothermia: unwanted effects
- Cardiovascular instability (arrhythmia)
- Coagulopathy
- Electrolyte disorders
- Increased risk of infections
## Hypothermia Trials 1993-2001

<table>
<thead>
<tr>
<th>Author</th>
<th>Target BT</th>
<th>Pat (n)</th>
<th>% fav Hyp</th>
<th>% fav Con</th>
<th>OR</th>
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<td>Clifton &amp; al. 1993</td>
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<td>Hirayama &amp; al. 1994</td>
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<td>38.1</td>
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<td>Meissner &amp; al. 1998</td>
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<td>Aibiki &amp; al. 2000</td>
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<td>Jiang &amp; al. 2000</td>
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<td>87</td>
<td>46.5</td>
<td>27.3</td>
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<td>Shiozaki &amp; al. 2001</td>
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<td>91</td>
<td>46.7</td>
<td>58.7</td>
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</table>

Adapted from: Maas AIR & al., Chapter 20, Head Injury, Hodder Arnold, London, UK 2005
Recent Hypothermia Trials

*Polderman & al. 2002: single center RCT*

136 patients with a GCS of 8 or less on admission in whom intracranial pressure (ICP) remained above 20 mmHg in spite of therapy according to a step-up protocol. Those who responded to the last step of our protocol (barbiturate coma) constituted the control group (n=72). Those who did not respond to barbiturate coma (n=64) were treated with moderate hypothermia (32-34 degrees C). Average APACHE II scores were higher (28.9+/−14.4 vs 25.2+/−12.1, p<0.01) and average GCS at admission slightly lower (5.37+/−1.8 vs 5.9+/−2.1, p<0.05) in the hypothermia group, indicating greater severity of illness and more severe neurological injury.
Recent Hypothermia Trials

► Polderman & al. 2002: single center RCT,

► Predicted mortality was 86% for the hypothermia group versus 80% in controls (p<0.01). Actual mortality rates were significantly lower: 62% versus 72%; the difference in mortality between hypothermic patients and controls was significant (p<0.05). The number of patients with good neurological outcome was also higher in the hypothermia group: 15.7% versus 9.7% for hypothermic patients versus controls, respectively (p<0.02).
Recent Hypothermia Trials

- **Gal & al. 2002**: single center RCT, 30 pts with severe TBI, mild hypothermia (34 °C), hypothermia (fav. 87%) better (p = .0843) than control (fav. 47%); ICP lower

- **Shiozaki & al. 2003**: single center case series, 22 pts w severe TBI and ICP > 40 mmHg during 34 °C were cooled to 31 °C (moderate hypothermia) – 100% mortality (19 brain deaths, 3 MOF deaths)
Recent Hypothermia Trials

Jiang & al. 2006: multi-center RCT, 215 pts with severe TBI, mild hypothermia for 5 vs 2 days. 5-day hypothermia (fav. 43.5%) better (p < .05) than 2-day hypothermia (fav. 29%); significant ICP rebound more frequently (p < .05) observed at re-warming after 2, but not after 5 days
Recent Hypothermia Trials

Hutchinson & al. 2008: multi-center RCT, 225 children, hypothermia (32 – 34 °C for 24 hours) vs. normothermia. Results better with normothermia: death 12% vs. 21% (p = .06) unfav. 22% vs. 31% (p = .14), more hypotension, more use of vasoactive medication with hypothermia
Recent Hypothermia Trials

- **Harris & al. 2009**: single center RCT, 25 pts randomized to control or treatment (brain hypothermia via “cooling cap”, to avoid side effects of whole-body hypothermia). Target temp. of 33 °C (brain) reached in only 2/12 patients. Mortality 50% (cap) vs. 31% (control); not significant (p = .43).

- One ongoing multi-center RCT (by Clifton & al.) will randomize 240 pts
Hypothermia: Open Questions

- Hypothermia is neuroprotective; it works well for patients on cardiopulmonary bypass, and it has been shown to be beneficial for patients after CPR

- Why, then, are we unable to demonstrate benefits for patients with severe TBI?
Hypothermia: Open Questions

› Target temperature too low? – most RCTs aimed for 32 - 34 °C. Increased risk of complications at hypothermia <34 °C

› Duration of hypothermia too short? – most RCTs used 24 – 48 hours. Increased risk of rebound ICP increase after short duration of hypothermia

› Re-warming too fast? – most RCTs allowed for 24 hours of re-warming
Hypothermia: Open Questions

- Hypothermia started too late? – Hypothermia works well if started prior to (CPB) or shortly after (CPR) the insult; much longer delay (4 – 8 hours) in TBI patients

- Hypothermia used for wrong indications? – intractable ICP

- Management problems? – especially in MRCTs if hypothermia is used in centers that have no experience with this
Hypothermia: Conclusions

Further studies are urgently required to determine optimal

- time to start cooling
- degree of hypothermia
- technique (whole-body vs. selective)
- duration of hypothermia
- duration of re-warming

Therapeutic hypothermia has no proven benefit after severe TBI
Facts about Hyperthermia

Fever

-occurs in up to 70% of TBI pts
-is attributable to infection in 50% of pts
-“central” fever in 20-30% of pts (?)
exacerbates inflammatory cascades
-increases neurotransmitter release and intracellular glutamate concentrations
-may lead to intracellular acidosis
Facts about Hyperthermia

- Brain temperature may be 0.5 – 2 °C higher than body core temperature
- This gap increases with higher BT
- Fever after severe TBI may be related to hypothalamic dysfunction
- Fever after severe TBI is associated with increased ICP, neurological impairment, and poor long-term outcome
Fever Control: Evidence

» Puccio AM & al. 2009: single center cohort study, 21 pts with induced normothermia (IV cooling) compared to 21 historic controls. ICP lower (12.7 vs. 16.4 mmHg), percentage of time with ICP >25 mmHg lower (p = .003), time with BT >38 °C 1.6% vs. 10.6% (p = .003).

» Hata JS & al. 2008: Cooling after TBI reduces systemic VO$_2$ only for non-shivering pts after TBI.
Side Effects of Fever Control

Schulman CI & al. 2005: single center trial, NO TBI pts, 82 ICU pts; 44 randomized to “aggressive” group, (treatment started at 38.5 °C), 38 to “permissive” group (treatment started at 40 °C). More infections (131 vs. 85, p = .26), more deaths (16% vs. 3%, p = .06) in the aggressive group. Study stopped during interim analysis. CONCLUSION: treating fever in ICU patients aggressively may lead to higher mortality rate.
Fever Control: Open Questions

► What should be monitored? – body or brain temperature

► What level of brain / body temperature is acceptable? – may be different for SAH vs. SDH with / without oedema

► With regard to fever - how long is the “vulnerable phase” of the injured brain? – 2 days, first week, 2 weeks???
Fever Control: Conclusions

- Hyperthermia may cause secondary brain insults and may worsen outcome after severe TBI
- Aggressive fever control in ICU patients may increase rate of infections and mortality
- There is no evidence to guide our treatment of patients with severe TBI
Conclusions

- The injured brain is most vulnerable after the impact
- Hyperthermia may occur early after severe TBI
- The risk of infection increases over time

The logical approach would be to
- treat fever more aggressively during the first few days
- Accept higher temperature after the first few days
Cooling: Practical Aspects

- **Pharmacologic agents**: require intact thermoregulation
  - Diclofenac, ibuprofen, acetaminophen

- **External cooling**: achieves heat loss by
  - Radiation: exposure of the skin
  - Convection: fan, cool-air blankets
  - Evaporation: water spray, sponge baths
  - Conduction: ice packs, cooling blankets

- Shivering must be prevented!
Cooling: Practical Aspects

- **Intravascular cooling:**
  - Infusion of 4 °C normal saline
  - Cooling devices (cold saline circulating through balloons around catheters)

- IV cooling devices and blanket cooling are most effective; goals are reached faster than with other techniques, BT is maintained more closely to target temp (closed loop technology)
Summary

- Hypothermia has no proven benefit
- Fever during the first days after severe TBI may impair outcome
- Normothermia should be maintained for the first few (3 – 7) days after TBI (= body temperature should not exceed 37.5 °C)
- After the first week fever should be treated less aggressively