Traumatic brain injury, therapeutic hypothermia and the POLAR trial

Tony Smith, Medical Director, St John
TBI and therapeutic hypothermia

- Quickly review treatment of TBI
  - Where therapeutic hypothermia currently ‘sits’
- Review evidence for hypothermia
  - Not an exhaustive literature search
- POLAR trial
- Questions
Traumatic brain injury

- Significant mortality and morbidity following trauma
- Largest cause of in-hospital mortality
- Largest cause of disability in survivors
- Enormous cost
  - The patient
  - Their family
  - Society
Treating patients with TBI

- Currently based on
  - Preventing secondary injury
  - Operating on mass lessons
  - Controlling ICP and optimising CPP (therapeutic hypothermia often used)

- No good evidence that we do makes a big difference
What we do know

▷ Steroids kill people
▷ Early decompressive craniectomy doesn’t help
  ▷ May make long term outcomes worse
▷ Hypertonic saline pre-hospital doesn’t help
▷ Hyperventilation probably makes outcomes worse
▷ Secondary injury makes outcomes worse
What we don’t know

› If treating ICP really helps
   › What ICP or CPP to target
› What ‘degree’ of secondary injury is important
   › Some attempts to reduce secondary injury may cause harm
› If hypothermia helps
   › If so, at what temperature and for how long
Hypothermia and TBI

We like to pretend we understand what is going on...

- Swelling, bleeding and bruising
- Altered autoregulation and blood flow
- ‘Leaky’ blood brain barrier
- White cell activation, inflammatory state and free radicals
- Activation of necrotic and apoptotic pathways

Hypothermia

- Reduces swelling and lowers ICP
- Reduces inflammatory response
- Lowers cerebral metabolic rate
Hypothermia and TBI

- Hypothermia also
  - Increases bleeding
  - Lowers cardiac output
  - Increases infection risk
  - Reduces gut activity
  - Reduces renal tubular function
  - Requires additional anaesthesia, equipment and nursing expertise
Hypothermia and other conditions

- Hypothermia improves outcomes
  - Following out of hospital cardiac arrest
  - Neonates with hypoxic ischaemic encephalopathy
- We cannot translate this evidence into patients with TBI
Evidence for hypothermia and TBI
Concluded

- No evidence for hypothermia to be routinely used
- No good evidence hypothermia improves outcomes
- Low quality trials produced the most apparent benefit
- High quality trials produced the least apparent benefit
### Cochrane 2009

**Review:** Hypothermia for traumatic head injury  
**Comparison:** Immediate hypothermia versus normothermia  
**Outcome:** Death at final follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hypothermia n/N</th>
<th>Control n/N</th>
<th>Odd Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelson 2005 HYPO1</td>
<td>4/25</td>
<td>4/25</td>
<td>1.00 [0.22, 4.54]</td>
</tr>
<tr>
<td>Adelson 2005 HYPO2</td>
<td>3/14</td>
<td>3/13</td>
<td>0.91 [0.15, 5.58]</td>
</tr>
<tr>
<td>Aibiki 2000</td>
<td>1/15</td>
<td>3/11</td>
<td>0.19 [0.02, 2.15]</td>
</tr>
<tr>
<td>Biswas 2002</td>
<td>3/8</td>
<td>0/6</td>
<td>8.27 [0.35, 197.61]</td>
</tr>
<tr>
<td>Clifton 1992</td>
<td>1/5</td>
<td>1/5</td>
<td>1.00 [0.05, 22.18]</td>
</tr>
<tr>
<td>Clifton 1993</td>
<td>8/23</td>
<td>8/22</td>
<td>0.93 [0.28, 3.16]</td>
</tr>
<tr>
<td>Clifton 2001</td>
<td>53/190</td>
<td>48/178</td>
<td>1.05 [0.66, 1.66]</td>
</tr>
<tr>
<td>Harris 2009</td>
<td>6/12</td>
<td>4/13</td>
<td>2.25 [0.44, 11.52]</td>
</tr>
<tr>
<td>Hashiguchi 2003</td>
<td>1/9</td>
<td>0/8</td>
<td>3.00 [0.11, 84.56]</td>
</tr>
<tr>
<td>Hirayama 1994</td>
<td>4/12</td>
<td>5/10</td>
<td>0.50 [0.09, 2.81]</td>
</tr>
<tr>
<td>Hutchison 2008</td>
<td>23/102</td>
<td>14/103</td>
<td>1.85 [0.89, 3.84]</td>
</tr>
<tr>
<td>Jiang 2000</td>
<td>11/43</td>
<td>20/44</td>
<td>0.41 [0.17, 1.02]</td>
</tr>
<tr>
<td>Marcon 1997</td>
<td>9/39</td>
<td>10/42</td>
<td>0.96 [0.34, 2.69]</td>
</tr>
<tr>
<td>Meissner 2003b</td>
<td>3/15</td>
<td>3/13</td>
<td>0.83 [0.14, 5.08]</td>
</tr>
<tr>
<td>Qiu 2007</td>
<td>9/40</td>
<td>13/40</td>
<td>0.60 [0.22, 1.63]</td>
</tr>
<tr>
<td>Shiozaki 1993</td>
<td>8/16</td>
<td>14/17</td>
<td>0.21 [0.04, 1.05]</td>
</tr>
<tr>
<td>Shiozaki 1999</td>
<td>0/8</td>
<td>0/8</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>Shiozaki 2001</td>
<td>8/45</td>
<td>6/46</td>
<td>1.44 [0.46, 4.55]</td>
</tr>
<tr>
<td>Smrcka 2005</td>
<td>5/35</td>
<td>11/37</td>
<td>0.39 [0.12, 1.28]</td>
</tr>
<tr>
<td>Yan 2001</td>
<td>13/24</td>
<td>16/20</td>
<td>0.30 [0.08, 1.15]</td>
</tr>
<tr>
<td>Zhang 2000</td>
<td>41/123</td>
<td>50/123</td>
<td>0.73 [0.43, 1.23]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 803 / 784  
Total events: 214 (Hypothermia), 233 (Control)  
Heterogeneity: Chi² = 21.31, df = 19 (P = 0.29); P = 13%  
Test for overall effect: Z = 1.44 (P = 0.15)
A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury

Samantha Crossley¹, Jenny Reid¹, Rachel McLatchie¹, Judith Hayton¹, Clair Clark¹, Margaret MacDougall² and Peter JD Andrews³*

Abstract

Introduction: Research into therapeutic hypothermia following traumatic brain injury has been characterised by small trials of poor methodological quality, producing variable results. The Cochrane review, published in 2009, now requires updating. The aim of this systematic review is to assess the effectiveness of the application of therapeutic hypothermia to reduce death and disability when administered to adult patients who have been admitted to hospital following traumatic brain injury.

Methods: Two authors extracted data from each trial. Unless stated in the trial report, relative risks and 95% confidence intervals (CIs) were calculated for each trial. We considered $P < 0.05$ to be statistically significant. We combined data from all trials to estimate the pooled risk ratio (RR) with 95% confidence intervals for death, unfavourable outcome, and pneumonia. All statistical analyses were performed using RevMan 5.1 (Cochrane IMS, Oxford, UK) and Stata (Intercooled Version 12.0, StataCorp LP). PooledRRs were calculated using the Mantel-Haenszel estimator. The random effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimators.

Results: Twenty studies are included in the review, while 18 provided mortality data. When the results of 18 trials that evaluated mortality as one of the outcomes were statistically aggregated, therapeutic hypothermia was associated with a significant reduction in mortality and a significant reduction in poor outcome. There was a lack of statistical evidence for an association between use of therapeutic hypothermia and increased onset of
Systematic review, Crit Care 2014

**Figure 2 Poor outcome at final follow-up.** (a) In total 20 trials involving 1,885 patients reported death, vegetative state, and long-term disability. When the results of 20 randomised controlled trials (RCTs) that evaluated poor outcome were statistically aggregated, therapeutic hypothermia was associated with a significant reduction in poor outcome (relative risk (RR) = 1.49, 95% CI = 1.27, 1.74, P < 0.00001). (b) Trials assessed as lower risk of bias: 16 trials, involving 964 patients, and assessed as lower risk of bias (domain-based assessment) were included in this analysis. When the results of 16 RCTs that evaluated poor outcome were statistically aggregated, therapeutic hypothermia was associated with a significant reduction in poor outcome (RR = 1.67, 95% CI = 1.45, 1.92, P < 0.00001).
Systematic review, Crit Care 2014

Concluded

- Some evidence to suggest hypothermia may be beneficial
- Majority of trials are of low quality
- Largest treatment effect in single center studies
- Smallest treatment effect in multi-centre studies

My conclusion

- Summary of the evidence, not useful for guiding treatment
- May be efficacious but not effective...
Huh?

- Efficacious
  - Works in an ideal world under ideal circumstances
- Effective
  - Works in the real world under usual circumstances

“*It’s not a great mission statement, but we’ll revise it if things get better.*”
So where does this leave us?

- Still a lot of uncertainty
- Too many small trials
- Too many single center trials
- The POLAR trial

I thought I was interested in uncertainty but now I'm not so sure.
The POLAR trial

The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT)

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2012 by Australian and New Zealand Intensive Care Research Centre

Sponsor:
Australian and New Zealand Intensive Care Research Centre

Collaborators:
Australian and New Zealand Intensive Care Society Clinical Trials Group
National Health and Medical Research Council, Australia
Victorian Transport Accident Commission
Monash University
Délegation à la Recherche Clinique et à l'Innovation (DRCi) CHU Besançon

Information provided by (Responsible Party):
Siouxzy Morrison, Australian and New Zealand Intensive Care Research Centre

Purpose

Traumatic brain injury (TBI) is a leading cause of death and long term disability, particularly in young adults. Studies from Australia have...
The POLAR trial

- Prospective randomised trial of prophylactic hypothermia in patients with severe TBI
- Multi-centre
- 500 patients
- Intervention: 33 degrees, 72 hours plus usual therapy
- Control: 36.5-37.5 degrees, 72 hours plus usual therapy
- Primary outcome is GOSE at 6 months
- Secondary outcomes
  - Mortality
  - Adverse events
  - Quality of life
The POLAR trial

Inclusion criteria
- GCS less than 9
- Age 18-60 years
- Intubated or about to be intubated

Randomisation can occur pre-hospital or in-hospital

Exclusion criteria
- Drugs or alcohol thought to be predominant cause of coma
- More than 3 hours since injury
- Intubated without drugs
- Shock
- GCS 3 and unreactive pupils
- Penetrating trauma
- Taking an anti-coagulant
The POLAR trial

- Monthly patient totals
- Cumulative total

Bar chart showing monthly patient totals and cumulative total from December 2010 to June 2014.
The POLAR trial

Recruitment by hospital admission

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfred</td>
<td>108</td>
</tr>
<tr>
<td>RMH</td>
<td>40</td>
</tr>
<tr>
<td>PAH</td>
<td>37</td>
</tr>
<tr>
<td>RPH</td>
<td>22</td>
</tr>
<tr>
<td>Auck</td>
<td>19</td>
</tr>
<tr>
<td>Waikato</td>
<td>2</td>
</tr>
<tr>
<td>Bes</td>
<td>19</td>
</tr>
<tr>
<td>Stras</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary

- Therapeutic hypothermia commonly used
  - Most commonly in response to ICP rise
- Evidence is not strong
  - There is reasonable rationale
  - There is a ‘signal’ trend in the evidence
- The POLAR trial may help
  - No single trial ever provides all of the answers
  - In danger of failing to recruit enough patients
Thank you

Tony.Smith@stjohn.org.nz