Pediatric Traumatic Brain Injury

Anne-Marie Guerguerian MD PhD
Assistant Professor of Critical Care Medicine & Pediatrics
Scientist in Neurosciences & Mental Health, Research Institute
Hospital for Sick Children, University of Toronto
Outline

• 2013 Update on interventional and observational trials in pediatric TBI
• Registered ongoing recruiting trials
• TBI importance: estimated economic burden
• Comparative effectiveness research
• International TBI Research Initiative
  – Who – when – why and what it means for patients and clinicians?
Brain directed therapy works

1. Active normothermia therapy
2. Active bedside application of brain directed therapy
Active hypothermia therapy vs. normothermia therapy

- As of 2013
- In children < 18 years
- With non fatal severe TBI admitted to PICU
- Who receive ICP monitoring guided care
- Active hypothermia therapy may be associated with higher risk of death
- Active normothermia therapy may be associated with lower mortality
<table>
<thead>
<tr>
<th>Study</th>
<th>Time to start cooling (mean hours)</th>
<th>Cooling (temperature target, probe site, duration)</th>
<th>Re-warming time</th>
<th>Compliance to cooling procedure (n/N [%])</th>
<th>Normothermia</th>
<th>Primary outcome</th>
<th>Global functional outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biswas et al (2002); single centre</td>
<td>4·6 (1·4)</td>
<td>32–34°C 48 h</td>
<td>12 h</td>
<td>8/10 (80%)</td>
<td>36·5–37·5°C</td>
<td>ICP</td>
<td>GOS, POPC, PCPC</td>
</tr>
<tr>
<td>Adelson et al (2005); multicentre</td>
<td>4·6 (1·1)</td>
<td>32–33°C 48 h</td>
<td>12–18 h</td>
<td>23/23 (100%)</td>
<td>36·5–37·5°C</td>
<td>Death + complication</td>
<td>GOS</td>
</tr>
<tr>
<td>Adelson et al (2005); single centre</td>
<td>15·0 (7·1)</td>
<td>32–33°C 48 h</td>
<td>12–18 h</td>
<td>14/14 (100%)</td>
<td>36·5–37·5°C</td>
<td>Death + complication</td>
<td>GOS, GOS-E</td>
</tr>
<tr>
<td>Hutchison et al (2008); multicentre</td>
<td>6·3 (2·3)</td>
<td>32–33°C 24 h</td>
<td>14–18 h</td>
<td>102/108 (94%)</td>
<td>36·5–37·5°C</td>
<td>Proportion with unfavourable outcome 6 months</td>
<td>PCPC</td>
</tr>
<tr>
<td>Adelson et al (2013); multicentre</td>
<td>5·1 (0·6)</td>
<td>32–33°C 48–72 h</td>
<td>42–54 h</td>
<td>37/39 (95%)</td>
<td>36·5–37·5°C</td>
<td>Death 3 months</td>
<td>GOS, GOSE-Peds</td>
</tr>
</tbody>
</table>

Hutchison Lancet 2013
Estimated risk of death with hypothermia vs. normothermia

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapeutic hypothermia</th>
<th>Normothermia</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Deaths</td>
<td>Total</td>
<td>Deaths</td>
</tr>
<tr>
<td>Biswas et al (2002)⁴</td>
<td>10</td>
<td>3</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Adelson et al (2005)³</td>
<td>23</td>
<td>2</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>Adelson et al (2005)³</td>
<td>14</td>
<td>3</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Hutchison et al (2008)⁵</td>
<td>108</td>
<td>23</td>
<td>117</td>
<td>14</td>
</tr>
<tr>
<td>Adelson et al (2013)¹</td>
<td>39</td>
<td>6</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>194</strong></td>
<td><strong>37</strong></td>
<td><strong>206</strong></td>
<td><strong>25</strong></td>
</tr>
</tbody>
</table>

Higher risk with normothermia  Higher risk with hypothermia

*Hutchison Lancet 2013*
Next steps: Function of survivors?

- Australia-NZ RCT results pending... *J. Beca et al*

- Upcoming patient level meta-analysis lead by John Beca to generate functional outcome estimates
  
  Hutchison et al + Adelson et al + Beca et al
Active bedside application of brain directed therapy works

Effect of implementation of a paediatric neurocritical care programme on outcomes after severe traumatic brain injury: a retrospective cohort study

Effect of implementation of a paediatric neurocritical care programme on outcomes after severe traumatic brain injury: a retrospective cohort study

Jose A Pineda*, Jeffrey R Leonard+, Ioanna G Mazotas, Michael Noetzle, David D Limbrick, Martin S Keller, Jeff Gill, Allan Doctor

Lancet Neurology 2013
Retrospective study design

• For children who have severe traumatic brain injury: ‘effect of a neurocritical care programme that was designed to implement a system of:

1. cross-specialty communication AND

2. an explicit plan of time sensitive + severity - based monitoring and intervention
Analyses

• Patient level outcomes
• Behaviour of the care team
  – by comparing the timing of invasive neuromonitoring and
  – intensity of therapies targeting intracranial hypertension and
  – programme performance
597 patients with trauma admitted to emergency department with GCS score ≤8

→ 316 without TBI or not admitted to PICU

281 met inclusion criteria

→ 157 excluded
- 80 abusive head trauma
- 27 GCS 3 and fixed and dilated pupils in emergency department
- 28 cardiac arrest before admission
- 22 gunshot wound to the head

124 analysed

→ 1 missing data from the medical record

63 before PNCP implementation

60 after PNCP implementation
Patient outcomes – before & after

Estimated probability of:

• Death declined after initiation of the PNCP from 21 % to 10 %
• Discharge to home without assistance increased from 10 % to 21 %
Probability of ICP monitoring

A

Number at risk
After PNCP 60 57 55 48 46 39 34 32 28 25 20 18
Before PNCP 63 57 52 41 31 26 24 20 17 12 9 4

PICU day
Intensity of care score

![Graph showing intensity of care score over days with significance levels for each day.](image)
Authors’ conclusion

• Programmatic change was associated with favorable outcomes
Interventional Studies
Traumatic brain injury | Recruiting | Interventional Studies | 33 Child, 157 Adult, 82 Senior | 162 studies
Attractive preclinical studies

• Cyclosporine  Mazzeo 2009
• Erythropoietine  Yatsiv 2005, Zhang 2009
• Progesterone  Xiao 2008
• Statins  Tapia-Perez 2008
• Vit D and/or Nutritional intervention  Prins 2009
• Neuro-restoration  Penn 2009
• Stem cells  Harting 2008
• Combination therapy with hypothermia therapy
Observational studies registered recruiting children (under-reporting)

- Vasospasm in Pediatric TBI
- The EPIC Project  Impact of Implementing the EMS TBI Treatment Guidelines
- The Differences Between Out-of-hospital Severe TBI (TBI) Treatment in a Physician-staffed Versus Paramedic-staffed Emergency Medical Service (EMS) Unit and Its Effect on Patient Prognosis
- Evaluating Use of Thromboelastography to Diagnose Coagulopathy After TBI
- Proteomics of Brain Trauma-associated Elevated Intracranial Pressure (ICP)
- Mild TBI Registry
- Evaluating a Novel Method of EEG Evoked Response Potential Analysis in Sport Concussion Assessment - Test Stability and Effect of Concussion
- Comparison of Brain Network Activation (BNA™) Analysis, Clinical Symptoms and Neuro-cognitive Performance in Concussed Children and Young Adults
- A Prospective Study of Brain Network Activation (BNA) Changes in High School Athletes Following Concussion
Observational Study Example

• Biomarkers in TBI in children
• J. Hutchison, ONF & VNI, CCCTG
• ~ 50% Recruitment planned 250
• Expected completion 2014
• Are there biomarkers associated with quality of life in paediatrics after TBI?

*(not registered in clinicaltrials.gov)
Comparative Effectiveness Research

• Why this is important for your practice and your patients
• Not a new concept – but has not been broadly applied in TBI
• Definition
• Expected costs & impact

2010 National Neurotrauma Workshop & Maas 2012
TBI – what’s making a difference or not in clinical research?

• Huge gap remains between successful preclinical neuroprotective agents and RCT results – 11% SFN 2013 abstract on TBI

• Guidelines for severe TBI based on ICP monitored guided care
  – None for mild or moderate where no ICP measured
  – Adherence to guidelines remains imperfect and we have not yet learned to efficiently modify measured variation in care practices
Average Estimated Costs Nonfatal Hospitalized TBI
Ages 0 to 17, USA 2005

<table>
<thead>
<tr>
<th>Age</th>
<th>Avg Medical Cost</th>
<th>Avg Work Loss Cost</th>
<th>Avg Combined Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>$51,147.71</td>
<td>$124,571.95</td>
<td>$175,719.7</td>
</tr>
<tr>
<td>5-9</td>
<td>$50,382.69</td>
<td>$123,661.41</td>
<td>$174,044.1</td>
</tr>
<tr>
<td>10-14</td>
<td>$56,262.05</td>
<td>$129,555.59</td>
<td>$185,817.6</td>
</tr>
<tr>
<td>15-19</td>
<td>$60,948.37</td>
<td>$129,760.28</td>
<td>$190,708.6</td>
</tr>
</tbody>
</table>

CDC WISQARS April 2012
### TBI costs affect the larger community

The potential solutions will have a broad impact

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<th>Ages</th>
<th>0 to 17, USA 2005</th>
<th>CDC WISQARS April 2012</th>
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<tbody>
<tr>
<td></td>
<td>Estimated Costs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medical &amp; Work</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lost Nonfatal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospitalized TBI</td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>$2,226,646,616.00</td>
<td></td>
</tr>
<tr>
<td>5-9</td>
<td>$1,321,161,176.00</td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td>$1,827,535,883.00</td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>$2,397,475,290.00</td>
<td></td>
</tr>
</tbody>
</table>

**Combined Cost**

$2,226,646,616.00

$1,321,161,176.00

$1,827,535,883.00

$2,397,475,290.00
Comparative effectiveness research – Definition

• Conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions = TBI

• Purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients type of severity = stakeholders > researchers

*Based on the American Department Health & Human Services Definition for CER
Methods applied in comparative effectiveness research

1. Systematic reviews of existing research, e.g., meta-analysis
2. Decision modeling, with or without cost information
3. Retrospective analysis of existing clinical or administrative data, including ‘natural experiments’
4. Prospective observational studies, including registries, which observe patterns of care and outcomes, without assigning patients to specific study groups
5. Experimental studies, including randomized clinical trials (RCTs), in which patients or groups of patients are assigned to alternative treatments, practices, or policies
International TBI Research Initiative

Global effort and funding

• Canadian Institutes of Health Research (9M CAD)
• European Commission (30M EUROs)
• National Institutes of Health
  – National Institute of Neurological Disorders and Stroke
  – Center for Information Technology
• DOD : US Department of Defence
InTBIR Objectives by 2020

• To coordinate and
• To harmonise clinical research activities across the full spectrum of TBI
• With the long-term goal of improving outcomes and lessening the global burden of TBI
InTBIR Objectives

- Establishing and promoting the use of harmonised, international standards for TBI clinical data collection
- Common Data Elements
Note: CIHR’s Institutes in Neurosciences and Mental Health are supportive of their use in research
InTBIR Objectives

• Creating a TBI patient registry by building common databases and linking them through an accessible, user-friendly interface for both entry and data search
InTBIR Objectives

• **Developing** and **applying** sophisticated analytical tools to enable Comparative Effectiveness Research (CER) for TBI

• Identify best practices in early diagnosis and treatment
InTBIR Expected Impact

• Expected results or return in a reasonable timeframe
• Expected effort vs. costs
• Expected patient impact timeline
• Knowledge translation
• What will it imply on a day to day basis for the patient and clinician
• Participation – participation - participation
TBI research needs going global

• More than multicenter trials or pragmatic trials
• Systematic application of research
• Common vocabulary
• Interdisciplinary
• Require strong and newer methodological paradigms for analyses
• Serve the patients more immediately
• Clinicians must become engaged stakeholders
Why clinicians must be engaged stakeholders?

• Must remain expert advocates for their unit’s programs of care, quality and research
• By becoming a clinician stakeholder
  – you drive expectations
  – receive regular results and interim reports
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