Trials and translations in traumatic brain injury

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Disclosures

PhD in translation of TBI research into practice at Monash University ANZIC RC

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TBI is prevalent, and expensive

- Global incidence of 100-700 per 100,000 population
- Leading cause of death and disability in children / young adults
- Global incidence increasing
  - More cars in low-middle income countries
  - More falls in aging populations of high income countries

- Total cost of TBI in Australia: $8.6 billion
  - Higher than dementia, bipolar, multiple sclerosis combined
  - Greater economic impact than workplace injuries

Access Economics 2009
TBI outcomes don’t seem to be improving
Lesson 1:

Evidence in TBI is generally low quality
Randomised trials for acute TBI

191 completed RCTs
- 69% had <100 patients (median n=66)
- 72% single centre

≥65% unclear/high risk in randomisation methods

26 robust RCTs across 18 interventions
- Multi-centre
- Low risk of bias
- n>100 (median 360)

19 (73%) showed no difference in patient-centred outcomes

Bragge et al, J Neurotrauma 2016
Guidelines for the Management of Severe Traumatic Brain Injury
4th Edition

- Of 189 studies, only 5 were “high quality RCTs”
- Level I Recommendations = 1
- Level II/III Recommendations = 20
Lesson 2:

Networks are essential to conduct high quality research in TBI
Network trials

- Of 5 “high quality” trials included in BTF Guidelines:
  - 4 were conducted by clinical trial networks:
  - 1 was not: National Acute Brain Injury Study: Hypothermia II
    - NIH-funded
    - Stopped by NIH early for lack of sites/poor recruitment
    - 49/97 (51%) enrolled at 1 site

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>No. of sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECRA</td>
<td>Australia, NZ, Saudi Arabia</td>
<td>15</td>
</tr>
<tr>
<td>CRASH</td>
<td>(UK) Europe, Asia, Latin America</td>
<td>239</td>
</tr>
<tr>
<td>SPIRIT ICU Study</td>
<td>France</td>
<td>6</td>
</tr>
<tr>
<td>BEST TRIPS</td>
<td>(USA) Latin America</td>
<td>6</td>
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</tbody>
</table>
# Networks do more than RCTs

## InTBIIR Network

<table>
<thead>
<tr>
<th>Region</th>
<th>Project</th>
<th>Focus</th>
<th>Budget (in M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (EC)</td>
<td>CENTER TBI</td>
<td>CER, Prognosis</td>
<td>€30.0 M</td>
</tr>
<tr>
<td></td>
<td>CREACTIVE</td>
<td>CER, Prognosis</td>
<td>€7.0 M</td>
</tr>
<tr>
<td>Australia (NHMRC)</td>
<td>OzENTER</td>
<td>CER</td>
<td>$0.3 M</td>
</tr>
<tr>
<td>USA (NIH)</td>
<td>TRACK-TBI</td>
<td>CER, Prognosis</td>
<td>$18.8 M</td>
</tr>
<tr>
<td></td>
<td>ADAPT Trial</td>
<td>CER</td>
<td>$16.1 M</td>
</tr>
<tr>
<td>Canada (CIHR)</td>
<td>mTBI in sport</td>
<td>CER, Diagnosis</td>
<td>$1.5 M</td>
</tr>
<tr>
<td></td>
<td>mTBI in children</td>
<td>Common Data Elements</td>
<td>$1.4 M</td>
</tr>
<tr>
<td></td>
<td>NeuroCare</td>
<td>Wearable monitoring in mTBI</td>
<td>$1.1 M</td>
</tr>
<tr>
<td></td>
<td>Melatonin in mTBI</td>
<td>RCT</td>
<td>$0.9 M</td>
</tr>
<tr>
<td></td>
<td>5P Study</td>
<td>Prognosis</td>
<td>$1.3 M</td>
</tr>
<tr>
<td></td>
<td>TBI Prognosis (CCCTG)</td>
<td>Cohort study in sTBI</td>
<td>$1.1 M</td>
</tr>
</tbody>
</table>
Lesson 3:

Networks should improve translation
Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review


- 13 recommendations assessed in 22 studies
- Adherence range 18-100%
  - Recommendations based on strong evidence (i.e. that developed by trial networks) are more likely to be implemented
  - Better adherence associated with better patient outcomes
- Networks improve implementation by generation of higher quality evidence
Translation of evidence via networks

- Traits of networked hospitals that facilitate translation:
  - Dedicated clinician-researchers on site:
    - Develop pragmatic, applicable interventional research
    - Invested in seeing results disseminated and implemented
    - Spillover to other clinicians
  - Centralised academic support: educators
  - Improved understanding of study design, strengths and limitations
• Engagement with Provider-Based Research Networks improves translation (in other settings: oncology, public health)

• Hospital characteristics not included in studies to date of adherence to evidence in neurotrauma

• Extrapolate from other critical care data?
Hammond et al, ICM 2015
Conclusions

• High quality evidence is the currency of translation
• Clinical trial networks are where money is made…
• …and (probably) where it should be spent.
Trials and translations in traumatic brain injury

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Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

**Conclusions**

Risk of death was significantly increased among patients with GCS scores of 3 to 8: 9 of 50 in the albumin group (18.0%) as compared with 3 of 51 in the saline group (6.0%) (relative risk, 3.00; 95% CI, 1.63 to 5.51; P<0.001). Among patients with GCS scores of 9 to 12, death occurred in 8 of 50 patients in the albumin group (16.0%) and 8 of 37 in the saline group (21.6%) (relative risk, 1.00). Among patients with GCS scores of 13 to 15, death occurred in 5 of 49 in the albumin group (10.2%) and 4 of 47 in the saline group (8.5%) (relative risk, 1.23; 95% CI, 0.50 to 3.02).

**Methods**

The Saline versus Albumin Fluid Evaluation study suggested that patients with traumatic brain injury who were resuscitated with albumin had a higher risk of death compared with those resuscitated with saline. We conducted a post hoc follow-up study of patients who were enrolled in the SAFE multicenter acute trauma register and who received saline. The subgroup of patients with GCS scores of 3 to 8 were classified as having severe brain injury, whereas those with GCS scores of 9 to 15 were classified as having moderate brain injury. The study objective was to compare mortality and functional outcomes at 1 month and 24 months post injury between patients who were resuscitated with albumin or saline.

Access Economics estimate:

- Complete implementation of SAFE TBI findings would save AUD $687 million