Rethinking neuroprotection in acute brain injury

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CCCF 2018
Conflicts of interest

• Nothing to declare
Outline

The importance of neuroprotection in ICU
Non-pharmacological targets
Neuroprotection at the bedside
Questions
The importance of neuroprotection in ICU

Non-pharmacological targets

Neuroprotection at the bedside

Questions
Neuroprotection: an important goal
Importance of differential pathophysiological mechanisms

STRUCTURE

- Macrovascular
- Microvascular
- Molecular

- Inflammation
- Receptor-mediated damage
- Oxidative damage
- Calcium-mediated damage

Maas AI et al. The Lancet Neurology 2008
Importance of differential pathophysiological mechanisms

Dynamic and PROGRESSIVE process following injury

Excitotoxicity
Mitochondrial dysfunction
Cortical depolarizations
Impaired autoregulation, reduced CBF
Impaired oxygen diffusion
Energy dysfunction
Edema
Inflammation
Neurodegeneration

TIME

Adapted from Stocchetti N et al. Crit Care 2013
Neuroprotective agents

Has this deflected attention from the development of neuroprotective strategies and trials addressing everyday ICU management such as optimal hemodynamic management?
Outcomes improving over time

• Despite repeated failures in pharmacological neuroprotection, outcomes for acutely brain injured patients have improved

• Secular trend in general critical care organization and delivery of care improvements over the past 2 decades

• It is likely that the organization of intensive treatment has contributed to this progress, offering a different kind of neuroprotection based on careful prevention and limitation of intracranial and systemic threats
Outline

The importance of neuroprotection in ICU

Non-pharmacological targets

Neuroprotection at the bedside

Questions
Alternative neuroprotective strategies
Non-pharmacological targets

**SECONDARY BRAIN INJURY**
- Ischemia
- Hypoxia
- Cerebral edema
- Inflammation
- Excitotoxicity
- Oxidative stress

**PRIMARY BRAIN INJURY**
- Extra-axial hemorrhages
- Cerebral contusions
- Diffuse axonal injury
- IVH

**SYSTEMIC THREATS**
- Hypoxemia
- Hypercapnia
- Hypotension
- Hyponatremia
- Pyrexia

**INTRACRANIAL THREATS**
- Expanding hematomas
- Contusions
- Intracranial HTN

**SECONDARY BRAIN INJURY**
- Ischemia
- Hypoxia
- Cerebral edema
- Inflammation
- Excitotoxicity
- Oxidative stress
Neurophysiologic targets

- Hypoxemia
- Hypotension
- Hypoglycemia
- Intracranial hypertension
- Fever
Identifying ICP targets

Treating ICP above 22 mm Hg is recommended. Values above this level are associated with increased mortality.
### Intracranial hypertension patterns

<table>
<thead>
<tr>
<th></th>
<th>&lt;20mHg</th>
<th>20-40mmHg</th>
<th>&gt;40mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good/mod recovery</strong></td>
<td>128 (69%)</td>
<td>73 (58%)</td>
<td>30 (30%)</td>
</tr>
<tr>
<td><strong>Severe disability</strong></td>
<td>23 (13%)</td>
<td>21 (17%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>34 (18%)</td>
<td>31 (25%)</td>
<td>55 (56%)</td>
</tr>
</tbody>
</table>
## Meta-analysis

**Summary:** Data suggest that ICP pattern, in particular **refractory ICP** and **response to treatment of raised ICP** are better predictors of neurological outcome than absolute ICP value.

<table>
<thead>
<tr>
<th>Meta-analysis OR (95% CI)</th>
<th>&lt;20mHg</th>
<th>20-40mmHg</th>
<th>&gt;40mmHg</th>
<th>Normal ICP</th>
<th>Raised ICP</th>
<th>Refractory ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vs Good</td>
<td>1.0 (ref)</td>
<td>1.6 (0.83-3.20)</td>
<td>2.3 (0.99-5.32)</td>
<td>1.0 (ref)</td>
<td>4.0 (2.27-7.04)</td>
<td>6.9 (1.13-42.83)</td>
</tr>
<tr>
<td>Good vs all else</td>
<td>1.0 (ref)</td>
<td>NR</td>
<td>0.19 (0.11-0.33)</td>
<td>1.0 (ref)</td>
<td>NR</td>
<td>0.01 (0.01-0.04)</td>
</tr>
</tbody>
</table>

Adapted from Treggiari et al. Neurocrit Care 2007
Are these two patients different?

PATIENT A

ICP 22

PATIENT B

ICP 20

Meyfroidt & Citerio. Neurosurgery 2017
Which patient are you more concerned about now?

PATIENT A

ICP 22

PATIENT B

ICP 9

ICP 20

Meyfroidt et Citerio. Neurosurgery 2017
Secondary brain insults
Increasing time spent at ICP level

Pressure*time burden of intracranial hypertension

ICP ‘dose’

Worse outcome

Güiza F et al Intensive Care Med. 2015
Assessment of cerebral autoregulation state

Ability to tolerate burden of intracranial hypertension
Assessment of cerebral autoregulation state

CA intact

150 mins

ICP 20mmHg
Assessment of cerebral autoregulation state

INABILITY to tolerate burden of intracranial hypertension

CA disrupted

15 mins

ICP 20mmHg
Avoidance of hyperthermia

• Numerous studies in patients with acute brain injury have shown links between fever and adverse outcome, regardless of the cause of fever

• Fever is an independent predictor of poor outcome in patients with ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage

• While repeated trials have reported that hypothermia offers no benefit, it is agreed that hyperthermia should be considered an insult

• Careful temperature monitoring and treatment of fever may therefore reduce further brain damage in the acute phase

Stochetti et al. Crit Care 2015
Bohman & Levine. Curr Opin Crit Care 2014
Polderman Lancet 2008
Fever burden

Temporal profile of body temperature in acute ischemic stroke: relation to stroke severity and outcome

Bartosz Karaszewski\textsuperscript{1,2}, Ralph GR Thomas\textsuperscript{1,3}, Martin S Dennis\textsuperscript{1} and Joanna M Wardlaw\textsuperscript{1,3}\*
Temperature AUC, maximum and final temperatures were associated with both NIHSS and modified Rankin Score at 3 months.
Outline

- The importance of neuroprotection in ICU
- Non-pharmacological targets
- Neuroprotection at the bedside
- Questions
Neuroprotection at the bedside

1. Detection of neurophysiologic targets at the bedside
   - Development of integrated neurophysiologic monitoring

2. Translation of these neuroprotective strategies at the bedside
   - Standardized management protocol
How do we visualize and interpret this data?

• Modern monitoring provides clinicians with continual stream of information
• Impossible to manually follow trends and changes across all screens
• Miss important trends and relationships
Integrative neurophysiologic platform

- Clinical neuro deterioration
- Systemic insults
- Intracranial volumes/oedema
- Pressure/Perfusion/Flow
- O₂ delivery/Metabolic
- Electrophysiologic function

- Serial clinical examinations
- ABP, O₂ sats, Temp, EtCO₂, Sodium, Glucose
- ICP, CT head
- CPP, TCD, Thermal diffusion probe
- PbrO₂/Microdialysis, SjVO₂
- EEG, SSEP

DATA INTEGRATION AND VISUALIZATION

Integration → Data display → Individualized Rx

Adapted from Citerio, Oddo et Taccone. Curr Opin Crit Care 2015
Integrative neurophysiology

- Improved understanding of fundamental mechanisms of secondary brain injury
- Identification of new therapeutic targets based on individual physiological parameters
- Novel understanding of the impact of interventions on physiological end-points and long-term cognitive function
Standardized management protocols
How can protocols improve patient care?

• Aims to improve outcomes by guiding consistent patient care:

  1. Facilitate communication
  2. Reduce cognitive load
  3. Coordinate the interdisciplinary team
  4. Increase the adoption of evidence-based interventions and improve adherence to guidelines
Neurophysiologic-driven protocols in TBI

Impact of ICU Structure and Processes of Care on Outcomes After Severe Traumatic Brain Injury: A Multicenter Cohort Study

Victoria A. McCredie, MBChB, PhD1,2,3; Aziz S. Alali, MD, PhD1; Damon C. Scales, MD, PhD1,3,4; Gordon D. Rubenfeld, MD, MSc1,4; Brian H. Cuthbertson, MBChB, MD1,4,5; Avery B. Nathens, MD, PhD3,6
Methods

• Design: Retrospective cohort study from 2011- 2013 linked with survey
• Setting: 134 ICUs in North America, 9,773 isolated severe TBI patients
• Exposure: Presence of a standardized TBI management protocol
  • Majority of protocols focused on the management of raised ICP and low partial pressure of brain tissue oxygen
• Primary outcome: in-hospital mortality
Standardized TBI management protocols were associated with improved risk-adjusted survival (OR 0.77; 95% CI 0.63-0.93)

<table>
<thead>
<tr>
<th>Description</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCC under United Council of Neurologic Subspecialties ICU director leadership</td>
<td>0.76 (0.63–0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Exclusion of neurotrauma NCC units</td>
<td>0.77 (0.64–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Closed NCC units only</td>
<td>0.77 (0.64–0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Patients transferred from a peripheral hospital removed (n = 5,772)</td>
<td>0.70 (0.55–0.88)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients transferred to skilled nursing facility classed as deceased (9,773)</td>
<td>0.81 (0.66–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Only hospitals with junior training programs (n = 5,513)</td>
<td>0.72 (0.52–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients with head Abbreviated Injury Score = 5a (n = 4,212)</td>
<td>0.58 (0.45–0.75)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Patients with Glasgow Coma Scale motor score &lt; 3a (n = 6,957)</td>
<td>0.78 (0.64–0.96)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Evidence-based protocols in AIS

Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial

Sandy Middleton, Patrick McElduff, Jeanette Ward, Jeremy M Grimshaw, Simeon Dale, Catherine D’Este, Peta Drury, Rhonda Griffiths, N Wah Cheung, Clare Quinn, Malcolm Evans, Dominique Cadilhac, Christopher Levi, on behalf of the QASC Trialists Group

Summary

Background We assessed patient outcomes 90 days after hospital admission for stroke following a multidisciplinary
Methods

• Cluster randomised controlled trial

• Randomised 19 Acute Stroke Units in New South Wales, Australia

• **Intervention units**: treatment protocols to manage
  1. Fever
  2. Hyperglycaemia
  3. Swallowing dysfunction

• Site-based education and support: multidisciplinary team building workshops to address implementation barriers
### Reaching neuroprotective targets

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>p value*</th>
<th>Difference in absolute change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=483)</td>
<td>Intervention (n=603)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean temperature during first 72 h in ASU (°C, ICC 0.084)</td>
<td>36.6 (0.30)</td>
<td>36.5 (0.27)</td>
<td>0.001</td>
</tr>
<tr>
<td>At least one temperature ≥37.5°C in first 72 h (ICC 0.009)</td>
<td>131 (27%)</td>
<td>105 (17%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glucose during first 72 h in ASU (mmol/L; ICC 0.056)</td>
<td>7.0 (2.0)</td>
<td>6.8 (1.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Swallowing screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swallowing screening within 24 h of admission to ASU (ICC 0.156)‡</td>
<td>24/350 (7%)</td>
<td>242/522 (46%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>13.7 (12.7)</td>
<td>11.3 (10.3)</td>
<td>0.144</td>
</tr>
</tbody>
</table>

Middleton et al. Lancet 2011
Protocol implementation strategy to support multidisciplinary teamwork focused on evidence-based management of key physiological variables delivers significantly better post-discharge outcomes for stroke patients.
In conclusion

- Our understanding of secondary brain injury mechanisms and physiologic responses to treatment is continually evolving.
- Moving forward, we must better understand whether these neurophysiologic parameters are modifiable, and whether modification affects relevant outcomes.
- Neurophysiologic monitoring at the bedside is a **DYNAMIC** process, not a single measurement.
- Integrated neuromonitoring may improve **situational awareness** and allow an **individualized approach** to therapy.
In conclusion

• Important physiological information obtained from several monitors may translate into outcome differences in select patients, but this benefit may not be universal.

• Aim to build collaborations between clinician researchers, computational neuroscientists, human factors engineering, translational scientists and biostatisticians.

• Using management protocols to provide evidence-based standardized care may be more practical targets for organizational quality-improvement initiatives.
Thanks

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Areas for further research

1. Explore ICP/CPP **practice pattern variation** (Synapse ICU, COMPARE)
2. Understand if **protocol-based neurophysiologic interventions** improve outcome (BOOST 3)
3. Evaluate if **individualized neurophysiologic targets** can be realized at the bedside (Cogitate, CONCEPT HIBI, COPILOT)
4. Explore whether the **design of data visualization** improves the translation of neuromonitoring-driven treatment paradigms (DECIPHER)