TRAUMATIC BRAIN INJURY
NOVEL AND EXPERIMENTAL THERAPIES

Objectives
- Briefly discuss magnitude of traumatic brain injury (TBI) as a public health problem
- Briefly discuss pathophysiology of TBI and identify potential therapeutic targets
- Discuss novel and experimental therapies for TBI
  - Hypothermia, Hyperoxia
  - Drug Therapies
    - Erythropoietin, Progesterone, Statins
  - Stem Cell Therapy

Abbreviations
- TBI – traumatic brain injury
- Epo – erythropoietin
- MAP – mean airway pressure
- CPP – cerebral perfusion pressure
- ICP – intracranial pressure
- CBF – cerebral blood flow
- HBOT – hyperbaric oxygen therapy

Public Health Problem
- Every day, >2000 children worldwide die from preventable injuries
- Injury is the #1 pediatric public health problem in the world WHO, 2008

Pediatric TBI
- Unintentional injury is the leading cause of death
- Traumatic brain injury is most often associated with death
- The annual total of TBI-related deaths is
  - More than 6X deaths related to HIV/AIDS
  - 20X deaths from asthma
  - 38X deaths from cystic fibrosis

Pediatric TBI (0-14 yrs)
- 2,174 Deaths
- 35,136 Hospitalizations
- 473,947 ER Visits
- 511,257 Pediatric TBI

CDC, 2002-2006
**Annual Burden**
- 80,000 new cases resulting in long term disability
- $56 billion/year aggregate lifetime cost

CDC, 2002-2006

**Pathophysiology**
- Primary Brain Injury
  - Occurs to the brain parenchyma at the time of injury
  - Contusion or shearing injury to axons
  - UNTREATABLE
- Secondary Brain Injury
  - Natural progression of injury
  - Cellular, biochemical and molecular pathways initiated by primary trauma
- THERAPEUTIC TARGET

**Standard Therapy**
- Prevent hypoxia, hypercarbia and hypotension
- Surgically manage extra-axial fluid
- Monitor and manage ICP/CPP
- Manage coagulopathy, glucose and electrolyte disturbances
- Manage/prevent seizures
- NEUROPROTECTION

**Hypothermia**
- “A man will survive longer in the winter than in the summer, whatever be the part of the head in which the wound is situated.”

-Hippocrates 460-377 BC

**Laboratory Evidence and Biological Rationale**
- Decrease BBB dysfunction
- Decrease cerebral edema
- Decrease levels of excitatory neurotransmitters and free radical formation
- Decrease cerebral metabolic rate
  - Each 1°C decreases CMR by 6-7%

**Adult Studies/Meta-analyses**
- Multiple meta-analyses of adult RCTs
- 12-19 RCTs
- Decreased or “trend towards” decreased mortality and improved neurologic outcomes
- Outcomes affected by depth and duration of hypothermia, and rate of rewarming
Hypothermia Complications

- Cardiac arrhythmias
- Coagulopathy
- Infections, esp. pulmonary
- Hypothermia-induced diuresis
- Electrolyte derangements

To cool or not to cool...

- 32.5°C for 24 hrs vs 37°C
- Initiated within 8 hours after injury
- DID NOT improve neurologic outcome
- Trend towards increased mortality and poor outcomes
- ICP lower during cooling and higher during rewarming
- MAP and CPP lower during rewarming

Study Shortcomings

- Heterogeneity of subjects
- Heterogenous protocols
  - Late induction
  - Short duration
  - Optimal temperature
  - Rewarming
- Co-interventions vary

Hypothermia

- Avoid hyperthermia
- Effective in decreasing ICP
- Relatively safe
- Early and prolonged
- 24 hr cooling does not improve outcome
- Slow rewarming
  - Rewarming to more than 37°C results in loss of autoregulation
- Second-tier therapy for intractable intracranial hypertension

Ongoing Trials

- Adults
  - POLAR (ANZICS-CTG)
  - NABIS (Clifton)
- Children
  - HiTBI Pilot (ANZICS)
  - CoolKids

Oxygen Therapy

- Decreased aerobic metabolism
- Impaired oxygen delivery
  - Arterial hypoxia
  - Reduction in CBF
- Mitochondrial failure
- Hypoxia in TBI associated with poor outcomes
Normobaric Hyperoxia (NBH)
- Small clinical trials (<20 patients)
- Increased brain tissue oxygen and decreased brain tissue lactate
- No change in lactate/pyruvate ratio

Hyperbaric Oxygen Therapy
- Administration of $O_2$ at pressure greater than atmospheric pressure at sea level (1 atm)
- 100% $O_2$ at 1.5-2.5 atm for 30-90 min
- Animal models:
  - Decreased edema
  - Decreased contusion volume

HBOT Complications
- Barotrauma (otic, sinus)
- Pneumonitis
- Tension pneumothorax
- Lowers seizure threshold
- Increased free radical production

HBOT Trials
- Fewer deaths
- Survivors were more severely disabled
- Current evidence does not support routine use

Ongoing Trials for Chronic TBI
- HBOT and SPECT Brain Imaging in TBI
  - Louisiana State University
  - Recruiting
  - Adults and Children
  - Treatment of Moderate to Mild Cognitive Dysfunction Caused by TBI with HBOT
  - San Antonio Military Medical Center
  - Enrollment by invitation

Drug Therapies
- Erythropoietin
- Progesterone
- Statins
Erythropoietin

- Glycoprotein hormone with erythropoietic and cytokine-like effects
- Expressed mainly in the kidney and liver
- EPO receptors widely expressed in the brain
  - EPO expressed in the brain and crosses BBB
- Endogenous neuroprotectant
  - Prevents neuronal apoptosis after cerebral ischemia

Biologic Rationale

- Cellular level
  - Reduces neuronal apoptosis
  - Anti-inflammatory
  - Stabilizes cells
  - Protective in other organs (hepatic ischemic-reperfusion injury, SCI, cardiac injury)
- Macroscopic level
  - Reduced post-traumatic brain edema
  - Reduced contusion volume
  - Reduced infarct size

Erythropoietin

- EPO binds to EPO-R
- Initiation of cascades leading to expression of anti-apoptotic genes and suppression of caspases

EPO Trials

<table>
<thead>
<tr>
<th>Design, N</th>
<th>Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talving 2010</td>
<td>Matched Case Control, 89 cases, matched 1:2</td>
<td>Variable Reduced in-hospital mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference in red cell transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference in morbidity*</td>
</tr>
<tr>
<td>Corwin 2007</td>
<td>RCT, 1,460 patients</td>
<td>40,000 IU SC qwk x3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased mortality in trauma subgroup</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference in red cell transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased thrombotic events</td>
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Ongoing Trials

- Effects of Epo on Cerebral Vascular Dysfunction and Anemia in TBI
  - Baylor
- EPO-TBI (ANZICS)
- Epo Effects after TBI
  - Wisconsin
- Safety of Darbepoietin Alfa Treatment in Patients with TBI
  - Univ of Alberta

Girls Do Better

- Female rats do better after TBI than males
- Female rats do even better at high progesterone conditions
- Male rats given progesterone did better
- Female TBI patients have better functional outcomes than males
**Progesterone**
- Steroid hormone
- Equilibrium with plasma levels in an hour
- Present in brain in small amounts
- Progesterone receptors throughout CNS

**Laboratory Evidence**
- Decreases brain edema and infarct size
- Attenuates free radical damage
- Reduces apoptosis
- Reduces inflammatory response
- Reduces excitotoxicity
  - Counteracts glutamate
  - Upregulates GABA or GABA receptors
- Attenuates neurological abnormalities after ischemia and spinal cord injury

**Progesterone Trials**

<table>
<thead>
<tr>
<th>Design, N</th>
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<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright, 2007 ProTECT RCT, 100 pts (77 Tx)</td>
<td>0.71 mg/kg x 1 hr, then 0.5 mg/kg/hr for 11 hrs, then 0.5 mg/kg/hr for 3 more days IV</td>
<td>No serious complications Not powered to detect benefit</td>
</tr>
<tr>
<td>Xiao, 2007 RCT, 159 pts</td>
<td>1 mg/kg q12h for 5d, IM</td>
<td>Reduced 6-mo mortality Improved 6-mo neuro outcomes No serious complications</td>
</tr>
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**Treatment Barriers**
- Adult phase II trials only
- Progesterone effect on a child?
  - Need separate trial to evaluate safety and effectiveness

**Ongoing Trials**
- Progesterone for TBI (ProTECT III)
  - Emory with 16 collaborating institutions
  - IV Progesterone within 4 hours, for 96 hours
  - Not yet recruiting

**Statins**
- HMG CoA reductase inhibitors
  - Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin
- Neuroprotective and restorative
- Cholesterol-independent ("pleiotropic effects")
- Reduced prevalence of Alzheimer's disease and vascular dementia
Pleiotropic Effects

- Anti-inflammatory
  - Suppress cytokine release
  - Interfere with leukocyte migration to CNS
- Vasoactive
  - Selective upregulation of endothelial nitric oxide synthase (eNOS)
  - Improves endothelial function
- Anti-oxidant
  - Reduce apoptosis and regulate progenitor cells for neurorepair
- Immune effects

In mice...

- Reduce hippocampal degeneration
- Improve cerebral blood flow after TBI
- Reduced functional neurological deficits

Statins and CNS Disease

- Potential therapy for ischemic stroke, Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, and some forms of retinal and eye diseases

Statin Side Effects

- Liver enzyme elevation
- Dose-dependent myopathy
  - Cerivastatin (2001) – taken off the market
- CoQ10 depletion
- Impair normal synaptic function and neuronal differentiation during brain development
- Associated with mood disorders
- Inhibit human placenta function

Ongoing Trials

- Effect of Rosuvastatin in Cytokines after TBI
  - San Luis Potosi, Mexico
- Mission Connect Mild TBI Integrated Clinical Protocol
  - Baylor

Stem Cells

- Cells capable of asymmetric division
- Pleuripotent
- Embryonic stem cells have greater potential to develop into different tissues (vs adult stem cells)
- Restorative therapy (vs protective)
Stem Cell

- Studies in animals
- Anecdotal reports in humans
- "Cell tourism websites"
  - www.stemcellspuhua.com
  - www.medra.com

Types of Stem Cells

- Embryonic (ESCs)
  - From embryos fertilized in vitro
  - Tendency to form teratomas
- Neural (NSCs)
  - From brain
  - Neurogenesis occurs in the subgranular zone of the dentate gyrus and subventricular zone

Types of Stem Cells

- Umbilical Cord
  - Use in treatment of cancer and genetic disorders (Krabbe disease, X-linked adrenoleukodystrophy, sickle cell, Hurler’s)
- Bone Marrow-Derived Adult Stem Cells
  - Hematopoietic (HSCs)
  - Mesenchymal (MSCs)

Mechanism of Benefit

- Unclear
- Transformation of cells into neurons
- Transformation of cells into neuroectodermal-derived cell types other than neurons
- Assist in blood vessel regeneration
- Production of trophic factors

Trials

- Safety of Autologous Stem Cell Treatment for TBI in Children
  - UT Houston
  - Completed
  - Bone marrow harvest (3 ml/kg) IV
  - Within 36 hours of injury

Discouraging Results

- Encouraging results from preclinical trials
- No pharmacologic agent has been proven to improve TBI outcomes
Hope for the Future

- Can potentially change outcomes
- Flaws in studies potentially altered results
- Multimodality vs single drug trials

Summary

- TBI is a major public health problem that results in significant morbidity and mortality.
- Understanding the pathophysiology facilitates identifying potential therapeutic targets.
- Success in preclinical trials for potential TBI therapies have not translated to success in clinical trials.

Summary

- Hypothermia, hyperoxia, erythropoietin, progesterone, statins and stem cells are among the interventions under study.
- Absence of evidence is not evidence of absence.
- Further studies are crucial to identify strategies that can improve outcomes.

Hypothermia References

- ECMM Meeting, February 2010, Keystone Colorado

Hyperoxia References

Epo References


Progesterone References


Statin References


Stem Cell References


Thank you. ☺