The Use of HBO for Persistent Symptoms after mTBI

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Disclosure

The views expressed in this presentation are those of the author and do not reflect official policy or position of the Department of Veteran Affairs or the U.S. Government.
Topic Outline

• Examining Theory – A Role for HBO in Persistent Symptoms after mild TBI

• Clinical Trials of HBO in Persistent Symptoms after mild TBI
Poll Question #1

- Which best describes your research experience?
  - have not done research
  - have collaborated on research
  - have conducted research myself
  - have applied for research funding
  - have led a funded research grant
Poll Question #2

- Which best describes your TBI research experience?
  - have not done research
  - have collaborated on research
  - have conducted research myself
  - have applied for research funding
  - have led a funded research grant
The Impact of TBI
Mechanisms of Injury - Sports
The Impact of TBI
Mechanisms of Injury - MVAs
The Impact of TBI
Mechanisms of Injury - Others
The Impact of TBI
Mechanisms of Injury - Military
Persistent Symptoms after mTBI

- Dizziness
- Loss of Balance
- Poor coordination
- Headaches
- Nausea
- Visual disturbance
- Light sensitivity
- Hearing difficulty
- Noise sensitivity
- Body/extremity numbness
- Altered taste or smell
- Appetite change
- Poor concentration
- Forgetfulness
- Difficulty making decisions
- Slowed thinking
- Fatigue
- Insomnia
- Feeling anxious
- Feeling depressed
- Easily irritated
- Poor frustration tolerance

Cicerone: J Head Tr Rehabil 1995;10(3):1-17
Overlap of Symptoms Complexes

- No Symptom Unique/Diagnostic for mTBI
- “Post-Concussive” Symptoms Present in “Normals”
- Symptoms Overlap with:
  - PTSD
  - Chronic Pain
  - Depression / Anxiety
  - Somatoform Disorders
  - Chronic Health Conditions
Persistent Symptoms after TBI Pathophysiology – The Cell’s Perspective
TBI Pathophysiology
The Cell’s Perspective

• Primary Insult Effects
  – Direct Mechanical Damage at Time of Insult
  – Respond to Preventive Measures

• Secondary Insult Effects
  – Delayed Non-Mechanical Effects
  – Respond to Treatment Measures
TBI Pathophysiology
The Cell’s Perspective

• Initial Stages of Injury
  – Direct Tissue Trauma
  – Impaired Blood Flow
    • CO₂ Responsiveness
    • Vasospasticity
    • Hyper / Hypoperfusion
  – Impaired Regulation Metabolism
    • Increased Cellular Work
    • Glucose / Lactate Imbalance
TBI Pathophysiology
The Cell’s Perspective

• Secondary Stages of Injury
  – Cellular Ischemia
    • Anaerobic Metabolism
    • ↑ Membrane Permeability
    • Edema Formation
  – Excitatory Neurotransmitters
    • Glutamate, Aspartate Release
    • Activation of NMDA / Ca\(^{++}\) / Na\(^{+}\) Channels

Journal of Special Operations Medicine Volume 9, Edition 4 / Fall 09
TBI Pathophysiology
The Cell’s Perspective

• Secondary Stages of Injury
  – Catabolic Intracellular Processes
    • Lipid Peroxidase, Protease, Phospholipase Activation
    • Free Radical & Free Fatty Acid Accumulation
    • Caspase & Calpain Mediated Cleavage

  – Cellular Apoptosis
TBI Pathophysiology
The Cell’s Perspective

• Cellular Level Injury
  – Cellular Metabolism
    • Intracellular Transport
  – Cellular Transmission
    • “Diffuse Axonal Injury”
    • Intracellular / Intercellular Communication
    • Intercellular Metabolic Transport
  – Both Neurons and Glial Cells Affected
Examining Theory – A Role for HBO in Persistent Symptoms after mTBI
Examining Theory
A Role for HBO in mTBI

Snake Oil

Science?

Politics
# Examining Theory

“Accepted” HBO Clinical Indications

<table>
<thead>
<tr>
<th>UHMS Accepted Indications</th>
<th>CMS Accepted Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Air or Gas Embolism</td>
<td>Gas Embolism</td>
</tr>
<tr>
<td>2 Decompression Sickness</td>
<td>Decompression Illness</td>
</tr>
<tr>
<td>3 Carbon Monoxide (± CN) Poisoning</td>
<td>Carbon Monoxide (± CN) Poisoning</td>
</tr>
<tr>
<td>4 Exceptional Blood Loss (Anemia)</td>
<td>N/A</td>
</tr>
<tr>
<td>5 Crush Injury, Compartment Syndrome, Other Acute Traumatic Ischemia</td>
<td>Crush Injury &amp; suturing severed limbs, Acute Traumatic Peripheral Ischemia, Acute Peripheral Arterial Insufficiency</td>
</tr>
<tr>
<td>6 Skin Grafts &amp; Flaps (Compromised)</td>
<td>Preparation &amp; Preservation of Compromised Skin Grafts (not primary)</td>
</tr>
<tr>
<td>7 Thermal Burns</td>
<td>N/A</td>
</tr>
<tr>
<td>8 Delayed Radiation Injury (Soft Tissue and Bony Necrosis)</td>
<td>Osteoradionecrosis and Soft Tissue Radionecrosis</td>
</tr>
<tr>
<td>9 Enhancement of Healing in Selected Problem Wounds</td>
<td>Diabetic Wounds of the Lower Extremity (with restrictions)</td>
</tr>
<tr>
<td>10 Clostridial Myositis and Myonecrosis (Gas Gangrene)</td>
<td>Gas Gangrene</td>
</tr>
<tr>
<td>11 Necrotizing Soft Tissue Infections</td>
<td>Progressive Necrotizing Infections</td>
</tr>
<tr>
<td>12 Osteomyelitis (Refractory)</td>
<td>Chronic Refractory Osteomyelitis</td>
</tr>
<tr>
<td>13 Intracranial Abscess</td>
<td>Actinomycoses</td>
</tr>
</tbody>
</table>
Examining Theory
Six Basic HBO Mechanisms

1) Diffusion and Mechanical Compression
2) Antibacterial Response Modulation
3) Correction of Cellular Hypoxia
4) Peripheral Vasoconstriction
5) Reperfusion Injury Modulation
6) Stimulation of Cellular Repair
# Examining Theory
## Potential HBO Applications to TBI

<table>
<thead>
<tr>
<th>HBO₂ Mechanism</th>
<th>Acute TBI</th>
<th>Chronic TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion and Mechanical Compression</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Modulation of Antibacterial Response</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Correction of Cellular Hypoxia</td>
<td>Likely</td>
<td>Possible</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Likely</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Reperfusion Injury Prophylaxis</td>
<td>Possible</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Stimulation of Cellular Repair</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Examining Theory
Proposed HBO Effects on TBI

• Reduction of Cerebral Edema
• Enhance Oxygen Availability to Revive “Penumbra” Neurons
• Influence Neurotransmitter Function / Availability (nitric oxide mediation)
• Immune Modulation
• Stem Cell Mobilization to Sites of Injury
Examining Theory
Proposed HBO Effects on TBI

• Bottom Line – Basic Science Still Lacking!
HBO for TBI Management

Clinical Trials
HBO Animal Research in TBI

• Systemic Review of Animal (Rodent, Cat, Dog) Research Supports HBO use in acute moderate to severe TBI
  – Reduces Acute Cerebral Edema
  – Reduces Markers of Cerebral Inflammation
  – Increases Cerebral Perfusion
  – Enhances Spatial Learning / Task Following

• Also in Chronic Moderate-Severe TBI
HBO in Animal TBI Research

- Animal Literature Caveats
  - HBO$_2$ Treatment Initiation
    - Animals Usually Minutes to ~ 2 Hours Post Injury
    - Humans Usually 6+ Hours to Days Post Injury
  - No HBO$_2$ Research in mTBI
  - No Direct Translation to Human Outcome
HBO in Human TBI Research

– Human Studies
  • Four Systematic Reviews of moderate-severe TBI
    – Included 23 publications (1972-2001)
    – Only four studies (382 subjects, 199 HBO₂ & 183 controls) met review criteria for scientific evaluation
    – Assessed acute, traumatic, moderate/severe TBI
    – Concluded current scientific evidence insufficient to prove effectiveness / ineffectiveness of HBO for TBI
  • 6 Clinical Trials Published in mTBI
HBO in Human TBI Research

- Overall Study Quality Assessed as Low*
- No Sham Therapy Included
- Randomization Inadequate*
- Blinding Not Used**
- Non-Standard Inclusion Criteria Across Trials

* Except Rockswold ‘10 Trial
** Except Rockwold ‘92 Trial
HBO in Human TBI Research

- Non-significant trend (P \leq 0.08) Favorable Outcome of full recovery or return to ADL 1.5 years post-injury
  - Three trials showed a significant reduction (RR 0.69, 95%CI 0.54-0.88) in risk of dying (mortality) with ‘numbers needed to treat’ being 7
  - No reduction in coma persistence or duration
- Effects on ICP and Pulmonary Status Only assessable secondary outcome measures
HBO in Human TBI Research

• Incidence of adverse events reported among 186 patients in 4 studies – 11.3%
  – Three Seizures – 1.6%
  – Fifteen Pulmonary Symptoms – 8%
  – Two Otic Barotraumas – 1.1%
HBO in Human TBI Research

• No scientifically rigorous research has been published in acute mild TBI or moderate TBI or chronic TBI of any severity (until last decade)
HBO in Human TBI Research

Clinical Trials of HBO for Persistent Symptoms after mTBI
## Clinical Trials

### US Air Force Trial (17DEC2008) – Completed

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Treatment of Moderate to Mild Cognitive Dysfunction Caused by Traumatic Brain Injury (TBI) with Hyperbaric Oxygen Therapy (HBOT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Col Robert Michaelson, Maj Gerald York, Col (ret) George Wolf</td>
</tr>
<tr>
<td>Sites</td>
<td>San Antonio Military Medical Center, San Antonio, Tx</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>19-60 years old, mild – moderate TBI, researcher confirmed diagnosis, stable status and medications</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized, Prospective, Sham Controlled, Single Blind  ( N = 50 )</td>
</tr>
<tr>
<td>Study Tests</td>
<td>ImPACT, ANAM, TOVA, PCL-M, fMRI, Biomarkers</td>
</tr>
<tr>
<td>Protocol Groups</td>
<td>Sham – 1.3 ATA Air (3 x 30 min, w / 10 min air breaks), 30 Exposures HBO2 – 2.4 ATA Oxygen (3 x 30 min, w / 10 min air breaks), 30 Exp</td>
</tr>
<tr>
<td>Findings</td>
<td>No b/n group differences of mTBI or PTSD sx’s or cognition. Improvements seen in both groups. 5% incidence minor AEs</td>
</tr>
</tbody>
</table>
# Clinical Trials

**Intermountain Health Care, Inc. (27JAN2009) – Completed**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Hyperbaric Oxygen Therapy in Chronic Stable Brain Injury (HYBOBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs</strong></td>
<td>Dr. Lin Weaver &amp; Susan Churchill, APRN-NP</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>LDS Hospital, Salt Lake City, Utah</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td>18-80 years old, chronic, stable, mild brain injury sequelae (secondary to stroke, anoxia or trauma), confirmed by questionnaires / testing</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Observational, Prospective, Unblinded, Self-Control Cohort</td>
</tr>
<tr>
<td><strong>Study Tests</strong></td>
<td>Neuropsychological testing, functional measures, health-related quality of life measures, and neurological examination, subjects own controls.</td>
</tr>
<tr>
<td><strong>Protocol Groups</strong></td>
<td>All subjects receive intervention (1.5 ATA oxygen, 60 minutes), 60 total sessions</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>No clinically meaningful improvements noted, however statistical improvements in symptoms reported in &gt;50%, and &gt;90% would like to participate in further HBOT trials.</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td>Churchill: UHM 2013;40(2)</td>
</tr>
</tbody>
</table>
# Clinical Trials

**International Hyperbaric Medical Foundation (15APR2010) – Completed**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Multicenter Observational Trial Hyperbaric Oxygen Therapy in Chronic Traumatic Brain Injury or Post-Traumatic Stress Disorder (NBIRIR-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Dr. James Wright &amp; Dr. Paul Harch</td>
</tr>
<tr>
<td>Sites</td>
<td>Multiple sites: currently 14 active, but number not specifically limited</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>18-65 years old, mild – moderate TBI or PTSD, diagnosis by any prior evaluation, 20% performance decrement on ANAM / “reaction time”</td>
</tr>
<tr>
<td>Study Design</td>
<td>Observational, Prospective, Unblinded, Self Control Cohort</td>
</tr>
<tr>
<td>Study Tests</td>
<td>Computerized neurocognitive, SPECT, QoL</td>
</tr>
<tr>
<td>Protocol Groups</td>
<td>All subjects receive intervention (1.5 ATA oxygen, 60 minutes), Plan 40 sessions, but extend “as indicated” to 60 – 80 sessions</td>
</tr>
<tr>
<td>Results</td>
<td>Improvements noted in Sx’s, cognition, QoL and SPECT scans</td>
</tr>
<tr>
<td>Reference</td>
<td>Harch: J Neurotrauma 2012;29(1)</td>
</tr>
</tbody>
</table>
# Clinical Trials

**VCU - VA - US Navy Trial** (06OCT2010) – **Completed**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Dr. David Cifu, CAPT Brett Hart, Michelle Nichols BSRN</td>
</tr>
<tr>
<td>Sites</td>
<td>Hunter Holmes McGuire VA Medical Center, Richmond, VA – Testing Naval Operational Medicine Institute, Pensacola, FL – HBO₂ Exposure</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>19-60 years old, chronic, stable, mTBI, researcher confirmed by questionnaires / testing</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized, Prospective, Double Blind, Sham Controlled</td>
</tr>
<tr>
<td>Study Tests</td>
<td>9 Symptom Assess, 12 Neuropsych, Computerized Posture, Eye Track</td>
</tr>
</tbody>
</table>
| Protocol Groups | Group A: 2.0 ATA (100% O₂ - 2.0 ATA Equivalent), 40 Sessions, 60 min  
                   Group B: 2.0 ATA (75% O₂ - 1.5 ATA Equivalent), 40 Sessions, 60 min  
                   Group C: 2.0 ATA (10.5% O₂ - 1.0 ATA Equivalent), 40 Sessions, 60 min |
| Results     | No b/n group differences of mTBI or PTSD sx’s or cognition. Improvements seen in both groups. 1% incidence minor AEs |
Clinical Trials

Cifu Study References:


**Clinical Trials**

<table>
<thead>
<tr>
<th><strong>Israeli mTBI Study– Completed</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Name</strong></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
</tr>
<tr>
<td><strong>Sites</strong></td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong></td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
</tr>
<tr>
<td><strong>Study Tests</strong></td>
</tr>
</tbody>
</table>
| **Protocol Groups** | Group 1 HBOT 1.5 ATA/60 min/40 sessions then no HBOT 2 mos  
Group 2 No HBOT 2 mos then HBOT 1.5 ATA/60 min/40 sessions |
| **Results** | No improvements during no HBOT/Crossover, but improvements in cognition, QoL and SPECT |
## Clinical Trials

**US Army MRMC Trial (24FEB2011) – Completed**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>A Pilot Phase II Study of Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (HOPPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Col Scott Miller, Dr. Lin Weaver, Susan Churchill APRN NP</td>
</tr>
<tr>
<td>Sites</td>
<td>Naval Hospital Camp Pendleton, CA; Evans Army Hospital, Ft.Carson, CO; Eisenhower Army Med. Center, Fort Gordon, GA</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>18-65 years old, Cohort 1 – PTSD, Cohort 2 – chronic, stable, mTBI, researcher confirmed by questionnaires / testing</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized, Prospective, ± Single Blind, Sham Controlled</td>
</tr>
<tr>
<td>N</td>
<td>72</td>
</tr>
<tr>
<td>Study Tests</td>
<td>RPQ, NSI, 19 Others Secondary, Dynavision, 6-Minute Walk Test</td>
</tr>
<tr>
<td>Protocol Groups</td>
<td>Cohort 1 and 2(a): PTSD or (b) mTBI, No Intervention, Local Care Cohort 2(c): mTBI, Active (1.5 ATA Oxygen, 60 min), 40 Sessions Cohort 2(d): mTBI, Sham Control (1.2 ATA Air, 60 min), 40 Sessions</td>
</tr>
<tr>
<td>Results</td>
<td>No b/n group differences of mTBI or PTSD sx’s or cognition. Improvements seen in both groups. 1% incidence minor AE’s.</td>
</tr>
<tr>
<td>Reference</td>
<td>Miller: JAMA Intern 2015;175(1)</td>
</tr>
</tbody>
</table>
HBO for Persistent Symptoms after mTBI – What Now?
Management of Persistent Symptoms of ….

- Multi-Modal Etiology
- Mechanism of Injury and Symptoms
- Site of Injury and Symptoms
- Severity of Injury and Symptoms
- Chronicity of Symptoms
  • Subject Characteristics

...Treat using standardized protocol!
Conclusions

• Mild TBI is a common Injury in civilian and military arenas
• Persistent Post-Concussive Symptoms are common
• Identifying Etiologies may be important, but is rarely conclusive.
• HBOT is NOT a recommended intervention for persistent symptoms after mTBI (or PTSD).
HBO for Persistent Symptoms following mTBI

Questions?

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