DoD Randomized Controlled Trials on the Efficacy of HBO₂ for mTBI

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Disclaimer

Opinions, interpretations, conclusions, and recommendations are those of the presenter and are not necessarily endorsed by the other members of the HBO₂ research consortium, the 4th Infantry Division, the U.S. Army Medical Materiel Development Activity, the U.S. Army Medical Research and Materiel Command, or the Department of Defense.
Agenda

- mTBI Background
- Literature Review
- Air Force Study – Wolfe et al
- Navy Study – Cifu et al
- HOPPS – Miller et al
- BIMA – Weaver et al
### Lethality of War Wounds among U.S. Soldiers.*

<table>
<thead>
<tr>
<th>War</th>
<th>No. Wounded or Killed in Action</th>
<th>No. Killed in Action</th>
<th>Lethality of War Wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revolutionary War, 1775–1783</td>
<td>10,623</td>
<td>4,435</td>
<td>42%</td>
</tr>
<tr>
<td>War of 1812, 1812–1815</td>
<td>6,765</td>
<td>2,260</td>
<td>33%</td>
</tr>
<tr>
<td>Mexican War, 1846–1848</td>
<td>5,885</td>
<td>1,733</td>
<td>29%</td>
</tr>
<tr>
<td>Civil War (Union Force), 1861–1865</td>
<td>422,295</td>
<td>140,414</td>
<td>33%</td>
</tr>
<tr>
<td>Spanish-American War, 1898</td>
<td>2,047</td>
<td>385</td>
<td>19%</td>
</tr>
<tr>
<td>World War I, 1917–1918</td>
<td>257,404</td>
<td>53,402</td>
<td>21%</td>
</tr>
<tr>
<td>World War II, 1941–1945</td>
<td>963,403</td>
<td>291,557</td>
<td>30%</td>
</tr>
<tr>
<td>Korean War, 1950–1953</td>
<td>137,025</td>
<td>33,741</td>
<td>25%</td>
</tr>
<tr>
<td>Persian Gulf War, 1990–1991</td>
<td>614</td>
<td>147</td>
<td>24%</td>
</tr>
<tr>
<td>War in Iraq and Afghanistan, 2001–present</td>
<td>10,369</td>
<td>1,004</td>
<td>10%</td>
</tr>
<tr>
<td>Nov. 2nd, 2015</td>
<td>52,312</td>
<td>5,363</td>
<td>10%</td>
</tr>
</tbody>
</table>

* Data are from the Department of Defense.1, 3

Gawanda, Atul MD. NEMJ Dec 2004/ http://icasualties.org/oif/ - DIOR
Survivability Improved

• Revolutionary War – 57% survived their wounds

• OEF/OIF Today – 90% survive their wounds

Body Armor Changes Injury Patterns and Survivability

**Armor**

Kevlar helmet
Up to 40 percent more resistant to penetration than steel helmets.

Interceptor vest
Outer Kevlar vest and inch-thick ceramic inserts. Removable throat and groin protectors.

Vulnerable Limbs, sides, and neck.

**Where Injured**

- Head: 33%
- Arms/hands: 40%
- Legs/feet: 37%

Most soldiers receive multiple injuries; totals add to more than 100 percent.
Mine Resistant Ambush Protected (MRAP)
Traumatic Brain Injury (TBI)

- “Signature Injury” of the Global War on Terrorism (GWOT) or Overseas Contingency Operations (OCO)

- Incidence: 320,000 with deployment related TBI – US 1.4 million
What is a traumatic brain injury?

A traumatic brain injury (TBI) is a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain. Not all blows or jolts to the head result in a TBI. The severity of such an injury may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury. A TBI can result in short or long-term problems with independent function.
## Classification of TBI

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural imaging</td>
<td>Normal</td>
<td>Normal or abnormal</td>
<td>Normal or abnormal</td>
</tr>
<tr>
<td>Loss of Consciousness (LOC)</td>
<td>0–30 min</td>
<td>&gt; 30 min and &lt; 24 hrs</td>
<td>&gt; 24 hrs</td>
</tr>
<tr>
<td>Alteration of consciousness/mental state (AOC)</td>
<td>a moment up to 24 hrs</td>
<td>&gt; 24 hours. Severity based on other criteria</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic amnesia (PTA)</td>
<td>0–1 day</td>
<td>&gt; 1 and &lt; 7 days</td>
<td>&gt; 7 days</td>
</tr>
<tr>
<td>Glasgow Coma Scale (best available score in first 24 hours)</td>
<td>13-15</td>
<td>9-12</td>
<td>&lt; 9</td>
</tr>
</tbody>
</table>

* Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be: looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and being unable to describe events immediately before or after the trauma event.

VA/DoD Clinical Practice Guideline
HBO₂ and Ischemic Penumbra

Brain ischemic penumbra – center region of brain death, surrounded by dysfunctional, but potentially viable tissue (penumbra), surrounded by normal tissue.

Therapy might favorably influence the ischemic penumbra.
WHEN TO TREAT

• Symptoms of mild TBI or concussion may resolve within hours to days or may improve over 1 – 3 months. However if symptoms persist and do not improve, medical treatment should be sought.

• All service members involved in a blast are seen to eliminate stigma.

• Risk of persistent symptoms increased with recurrent concussions.
VA/DoD Clinical Practice Guideline for
Management of Concussion/mild-Traumatic Brain Injury

A: Initial Presentation

1. Person injured with head trauma resulting in alteration or loss of consciousness (possible mTBI)
   (See sidebar 1) [A-1]

2. Urgent/emergent conditions identified?
   (See sidebar 2) [A-2]

3. Refer for emergency evaluation and treatment

4. Evaluate for diagnosis of concussion/mild-TBI based on history
   (See sidebar 3) [A-3]

5. Is the diagnosis moderate or severe TBI?

6. Exit algorithm

7. Are concussion/mTBI with related symptoms present?
   (See sidebar 4) [A-4]

8. Is person currently deployed on military or combat operation?
   [A-5]

9. Follow guidance for management of mTBI in combat or ongoing military operation (deployment)

10. Is person presenting immediately after injury (within 7 days)?
   [A-6]

11. Follow local guidance or ED protocols for management of acute mTBI in non-deployed/civilian patients

12. Is person currently on treatment for mTBI symptoms?
    [A-7]

13. Go to Algorithm B Management of concussion/mTBI symptoms

14. Go to Algorithm C Follow-up persistent symptoms of concussion/mTBI

Sidebar 1 - Possible Causes for Head Trauma
- Blast or explosion
- Head striking or being struck by object, or fall
- Undergoing acceleration/deceleration movement (e.g., Motor vehicle accident)
  [A-1]

Sidebar 2 - Indicators for Immediate Referral
1. Current altered consciousness
2. Progressively declining neurological exam
3. Pupillary asymmetry
4. Seizures
5. Repeated vomiting
6. Double vision
7. Worsening headache
8. Cannot recognize people or disoriented to place
9. Behaves unusually or confused and inattentive
10. Blurred speech
11. Unsteady on feet
12. Weakness or numbness in arms/legs

Sidebar 3 - Diagnostic Criteria for Concussion/mild TBI
- Loss of or a decreased level of consciousness for less than 30 minutes
- Loss of memory for events immediately up to a one day after the injury
- Alteration of consciousness/mental state for 0-24 hours after the injury
- Normal structural imaging
- Glasgow Coma Score: 13-15 (best value within first 24 hours if available)
  [A-3]

Sidebar 4 - Post-Concussion/mTBI Related Symptoms
* Symptoms that develop within 30 days post injury

Physical Symptoms:
- Headache, dizziness, balance disorders, nausea, fatigue, sleep disturbance, blurred vision, sensitivity to light, hearing difficulties, sensitivity to noise, seizures, transient neurological abnormalities, numbness tingling

Cognitive Symptoms:
- Attention, concentration, memory, speed of processing, judgment, executive control.

Behavior/Emotional Symptoms:
- Depression, anxiety, agitation, irritability, impulsivity, aggression.
VA/DoD Clinical Practice Guideline for Management of Concussion/mild-Traumatic Brain Injury

B: Management of Symptoms

1. Person diagnosed with concussion/mTBI [B-1]
2. Complete history and physical examination/ lab tests, MSE and psychosocial evaluation [B-2]
3. Clarify the symptoms [See sidebar 5] [B-3]
   - Build therapeutic alliance [B-4]
4. Evaluate and treat co-occurring disorders or diseases (such as mood, anxiety, stress or substance use disorders)
5. Determine treatment plan [B-5]
6. Educate patient/family on symptoms and expected recovery (See sidebar 6) [B-6]
7. Provide early interventions [B-7] (See sidebar 6)
8. Are all symptoms sufficiently resolved within days? [B-8]
   - No
     - Initiating symptom-based treatment [B-8]
     - Consider case management (See sidebar 7)
9. Follow-up and reassess in 4-6 weeks [B-9]
10. Are all symptoms sufficiently resolved? [B-10]
    - Yes
      - Follow-up as needed
      - Encourage & reinforce
      - Monitor for comorbid conditions
      - Address:
        - Return to work/duty/activity
        - Community participation
        - Family/social issues
    - No
      - Continue on Algorithm C: Management of Persistent concussion/mTBI symptoms

Sidebar 5: Symptom Attributes
- Duration of symptom
- Onset and triggers
- Location
- Previous episodes
- Intensity and impact
- Previous treatment and response
- Patient perception of symptom
- Impact on functioning [B-3]

Sidebar 6: Early Intervention
- Provide information and education on symptoms and recovery
- Educate about prevention of further injuries
- Reassure on positive recovery expectation
- Empower patient for self management [B-6]
- Provide sleep hygiene education
- Teach relaxation techniques
- Recommend limiting use of caffeine/tobacco/alcohol
- Recommend graded exercise with close monitoring
- Encourage monitored progressive return to normal duty/work/activity [B-7]

Sidebar 7: Case Management
- Assign case manager to:
  - Follow-up and coordinate (remind) future appointments
  - Reinforce early interventions and education
  - Address psychosocial issues (financial, family, housing or school/work)
  - Connect to available resources
1. Person diagnosed with concussion/mTBi and persistent symptoms beyond 4-6 weeks not responding to initial treatment (C-1)

2. Reassess symptoms severity and functional status. Complete psychosocial evaluation (See sidebar 8) (C-2)

3. Are symptoms and functional status improved?
   - Yes
   - No


5. Encourage and reinforce. Monitor for comorbid conditions.

6. Follow-up and reassess in 3 to 4 months (C-8)

7. Assess for possible alternative causes for persistent symptoms; Consider behavioral component (e.g., sleep or a mood disorder) (C-3)

8. Any behavioral health disorders diagnoses established? (Depression, traumatic stress, anxiety, or substance use disorder) (C-4)
   - Yes
   - No

9. Manage comorbidity according to VA/DoD practice guideline for behavior health conditions.

10. Consider referral to mental health for evaluation and treatment (C-5)

11. Any persistent symptoms (Physical, cognitive or emotional) (C-6)
   - Yes
   - No

12. Refer for further evaluation and treatment.

13. Consider referral to occupational/vocational therapy and community integration programs. Continue case management (C-7)

Sidebar 8 - Psychosocial Evaluation

1. Support system
2. Mental health history
3. Co-occurring conditions (chronic pain, mood disorders, stress disorder, personality disorder)
4. Substance use disorder
5. Secondary gain issues (Compensation, litigation)
6. Unemployment or change in job status
No definitive treatment

• Testimonials
  – Harch Hyperbarics - http://www.hbot.com/
  – Rocky Mountain Hyperbaric Institute – http://rockymountainhbot.com/

• Lobbyist and patient advocacy groups

• Political pressure on DoD to provide this possible definitive treatment for ALL wounded Warriors with TBI
Consensus Conference

Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury and Defense and Veterans Brain Injury Center

Consensus Conference on

Cognitive Rehabilitation for Mild Traumatic Brain Injury

27 and 28 April 2009, Washington, DC

• H.R. 4568: TBI Treatment Act
  – Rep. Peter Sessions (R-TX)
  – Appropriate funds to empirically treat all service members and veterans with TBI
Oklahoma Takes the Lead in Recognizing TBI Treatments for Veterans

07 May 2014
0 Comments
in 2014 Session Update, Legislation, Veterans
by Mark Allen

SB 1604, The Oklahoma Veterans Traumatic Brain Injury Treatment and Recovery Act of 2014, authored by Senator Mark Allen and Representative John Bennett, was signed into law yesterday by Governor Mary Fallin. The bill goes into effect November 1, 2014.

The first of its kind in the country, the bill states that any Oklahoma veteran who has been diagnosed with a traumatic brain injury (TBI) and prescribed hyperbaric oxygen treatment (HBOT) by an authorized medical professional may receive HBOT at any facility in the state that has a hyperbaric chamber.

Hyperbaric chambers offer oxygen at a level higher than atmospheric pressure. Studies show the 100 percent oxygen chambers trigger the brain’s neurons and harness the healing power of oxygen.

Subject to the availability of funding, the treatment will be paid for with private dollars at no cost to the veteran.
Two Approaches

- The population at risk for TBI was not co-located where the DoD had hyperbaric medicine
  - Take Service Members to the chambers…
  - Take chambers to the Service Members…
Challenges to studying the efficacy HBO$_2$ for mTBI

- Frequent lack of pre-injury baseline data
- Complicated by polypharmacy
- Significant time commitment (8 + weeks)
- Post-traumatic stress disorder (PTSD) is a common co-morbid condition
- Refractory patients hesitant to get placebo or “sham” arm of an RCT
HBO$_2$ for Acute TBI

- **1967**: K.H. Holbach (Germany), begins treating severe, acute TBI and CVA
  - 2-3 atm abs, 30-60 minutes
  - Saw improvement in EEG, biochemical markers, rCBF
- **1976**: Artru, Chacornac, Deleuze (France); RCT, 60 patients
  - 2.5 atm abs, 60 minutes, daily for 10 days, 4 days off, repeated until patient died or regained consciousness
  - No difference in mortality at 12 months
  - Trends toward improvement in duration of coma with HBO$_2$, but not statistically significant
- **1983-94**: Rockswold, Ford, et al.; RCT in acute, severe TBI
  - 1.5 atm abs, every 8 hours, until subject awake or brain dead
  - HBO$_2$ improved mortality
  - Worse functional outcome in HBO$_2$ group
- **2001**: Rockswold, et al. HBO$_2$ on physiological measures, no control group
  - 1.5 atm abs daily for 6 days
  - Improvements in cerebral blood fall and intracranial pressure
- **2009**: Rockswold, et al; RCT
  - HBO$_2$ improved biochemical markers
History of HBO2 at 1.5 atm abs for brain injury

• 1973: Holbach and Caroli, Bonn, Germany
  – From 1967 to 1973, over 700 HBO2 sessions for acute brain injury (stroke & TBI),
  – Examined cerebral glucose metabolism and acid/base balance of the brain in 102 patients that received 267 courses of HBO2
    • Discovered that 1.5 atm abs was optimal, 2.0 atm abs was adverse
• 1976: Holbach, Wassman, and Hoheluchter
  – Used 1.5 atm abs for chronic stroke
• 1980: Neubauer and End, Florida
  – Used 1.5 atm abs for chronic stroke, 2.0 atm abs for acute stroke
  – Subsequently used 1.5 atm abs for other types of chronic brain injury
• 1994: Harch abstract
  – SPECT brain imaging and “low pressure HBOT” for treatment of chronic brain injury (including TBI)
History of HBO2 at 1.5 atm abs for brain injury

• 2004: Barrett et al. UHM; 31:395-406
  – Single-center prospective, non-randomized study
  – 5 subjects 3 years post-brain injury 120 HBO2 exposures at 1.5 atm abs
  – No significant objective changes

  – 252 with symptomatic brain injury with positive SPECT at least 1 mos post injury
  – 20 HBO2 exposures at 0.1 Mpa with 96% oxygen
  – 160 subjects with “normal” SPECT, 92 of persistent abnormals had improved blood flow

  – Rat model of chronic traumatic brain injury.
  – Control, sham, HBO2 at 1.5 atm abs x 90 min BID for 80 sessions
  – Improvement in spatial learning and increased vascular density in the hippocampus
Open Label Data from Non-Randomized Case Series at 1.5 mTBI

• 2011: Harch et al. J. of Neurotrauma; 28:1–18
  – 16 Veterans 1-4 years post TBI with chronic symptoms
  – exposed to HBO$_2$ 1.5 ATA x 40 days with twice daily dive sessions
  – ~ 10 % improvement in memory and neuropsych tests
  – Up to 51% improvement in self-reported anxiety and depression scores
  – Self-reported ‘improved to normal’ cognition (50→67%), emotional (32→61%); physical (47→66%)
  – Brain SPECT scans showed improved metabolism after HBO$_2$
  – Assessment immediately post rx; No data on durability of response
  – Design does not allow assessment of contribution of HBO$_2$, and results are in range of placebo/ Hawthorne effect
UHMS and HBO for mTBI

• Position Statement

Currently available scientific literature does not support an endorsement of HBO\textsubscript{2} for chronic brain injury and recommended prospective, randomized, and controlled clinical trials to assess whether HBO\textsubscript{2} therapy is associated with favorable risk-benefit and cost-benefit ratios for TBI.
“Although they are cited frequently, the case series and time-series studies of HBO_2 for TBI patients had serious flaws. There were no high-quality studies of the use of HBO_2 to improve function and quality of life in patients with chronic, stable disabilities from TBI. The most important gap in the evidence is a lack of a good quality time-series study or controlled trial of the effects of HBO_2 on cognition, memory, and functional status in patients with deficits due to mild and moderate chronic TBI.”
“The US Department of Health and Human Services Centers for Medicare and Medicaid Services (CMS) limits reimbursement for HBO2 therapy to that which is administered in a chamber for the indications listed in Table 1. CMS does not authorize HBO2 as standard of care for TBI, nor is it a reimbursable benefit for civilian providers by third party payers.”
“The routine application of HBOT to these patients cannot be justified from this review. Given the modest number of patients, methodological shortcomings of included trials and poor reporting, the result should be interpreted cautiously. An appropriately powered trial of high methodological rigour is required to define which patients, if any, can be expected to benefit most from HBOT.”
HBOT in mTBI/PPCS Study 2014

INTRODUCTION

By Cara J. Rowe on March 24, 2014

FEBRUARY, 2014

LSU IRB #7381

Welcome and thank you for your interest in the above study. The study is an investigation of hyperbaric oxygen therapy at 1.5 ATA (HBOT 1.5) in the treatment of mild traumatic brain injury (mTBI) persistent post-concussion syndrome (PPCS) resulting from either blunt or blast injury in both military and civilians. The study is to be conducted at Louisiana State University Health Sciences Center-New Orleans (LSUHSC-NO), and Oklahoma State University Health Sciences Center (OSUHSC) in

https://www.clinicaltrials.gov/ct2/show/NCT02089594?term=HBOT+MTBi+PPCS&rank=1
HBO$_2$ for chronic impairments due to TBI, RCT

• 2013: Boussi-Gross, et al.
  – N=90; PCS from mild TBI; 1 to 6 yrs post-injury
  – Randomized to HBO2 v Control (no sham), then the Controls exposed to HBO2 two months later
  – HBO2 – 1.5 ATA x 60 (90) min x 40 sessions
  – Significant improvement in ALL cognitive measures and Quality of Life (p<0.005).
  – Brain SPECT showed improved brain metabolism after HBO2
The Effect of Hyperbaric Oxygen on Symptoms Following Mild Traumatic Brain Injury

2012: Wolf G. et al; J Neurotrauma
U.S. Air Force School of Aerospace Medicine (USAFSAM)

- Blinded RCT of 50 Service Members with post concussive symptoms after 1 or more concussions: 1.3 air vs. 2.38 atm abs HBO2
- Outcome measures before and after 30 daily sessions; and 6 weeks later
  - Computer neurocognitive tests: ImPACT, Braincheckers –ANAM, TOVA
  - Symptoms: ImPACT and PCL-M
- Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) and Post-traumatic Disorder Checklist-Military (PCL-M), ImPact total score - no difference with HBO2, but both groups improved more than expected.
- Why did the sham group improve?
  - Placebo effect, Hawthorne Effect
  - Daily interactions with staff
  - Physiological effects of increased partial pressures of N2 and O2
The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms

2013: Cifu D. et al; J Head Trauma

Courtesy, Capt. Hart, Dr. Cifu
Navy-VCU-NOMI: Participants/Intervention

- Active duty, hx mTBI 4 months to 2 years prior, still having post concussive symptoms
- 60 subjects randomly assigned to 1 of 3 chamber groups (all subjects pressurized to 2.0 atm abs)
  - #20 - 2.0 atm abs oxygen equivalent (100% O2 / 0% N2)
  - #20 - 1.5 atm abs oxygen equivalent (75% O2 / 25% N2)
  - #20 - 1.0 atm abs air equivalent (10.5% O2 / 89.5% N2)
- 12 subjects tested/began chamber sessions every 2.5 months
- 40 sessions per subject (8 weeks), 1 chamber exposure/day
128 Screened for Eligibility

59 Excluded
  30 Refused to Participate
  29 Failed to Meet Inclusion Criteria

61 Randomized

21 Randomized to Sham Condition
  21 Received Intervention as Assigned
  21 Assessed at 2-week Follow-Up
  20 Assessed at 12-week Follow-Up
  1 Lost to Follow-Up; Not located
  21 Included in This Analysis

21 Randomized to 1.5 ATA Condition
  21 Received Intervention as Assigned
  21 Assessed at 2-week Follow-Up
  20 Assessed at 12-week Follow-Up
  1 Lost to Follow-Up; Declined Participation
  21 Included in This Analysis

19 Randomized to 2.0 ATA Condition
  19 Received Intervention as Assigned
  18 Assessed at 2-week Follow-Up
  1 Lost to Follow-up; Unavailable
  19 Assessed at 12-week Follow-Up
  19 Included in This Analysis
Navy-VCU-NOMI: Participants/Intervention

• Assessment Schedule:
  – Baseline
  – After completion of chamber sessions (2 month)
  – 3 months later (5 months post-enrollment)

• Assessment battery requires 5 hours:
  – Symptom Questionnaires
  – Structured interviews
  – Neuropsychological
  – Neurophysiological (Eye Tracker, Balance)

• No difference in symptoms by allocation, but apparent improvement in many

Courtesy, CAPT Hart, Dr. Cifu
Results

• **No differences between any of the groups** on any aspect of the **primary** outcome measure (RPQ), including subscales RPQ-3 and RPQ-13
  – Within group comparisons (pre/post intervention) were not significant

• **No differences between any of the groups** on the total score of the **secondary** measure (PCL-M)
  • Within group differences showed improvement (pre/post):
    • Sham: 6.7 point improvement
    • HBO₂ 1.5 ATA: 6.2 point improvement
    • HBO₂ 2.0 ATA: 13.9 point improvement (statistically improved)

One-way ANOVA conducted on total RPQ score, subscales RPQ-3 and RPQ-13, and all individual items

One-way ANOVA conducted on total PCL-M score

*Courtesy, CAPT Hart, Dr. Cifu*
Results

RPQ Sub-analysis: Within group differences on individual symptoms

• Sham group (air equivalent) showed no significant differences between pre/post compression scores
• 1.5 ATA equivalent group showed a significant increase (worsening) in light sensitivity
• 2.0 ATA equivalent group showed a significant decrease (improvement) on noise sensitivity and frustration/impatience
• No trends in HBO$_2$ dose indentified

Courtesy, CAPT Hart, Dr. Cifu
Results

PCL-M Sub-analysis: Within group differences on individual symptoms

- Sham group showed significant improvement on super alertness/watchfulness and being easily startled between pre-post compression scores
- 1.5 ATA equivalent group showed a significant improvement on super alertness/watchfulness
- 2.0 ATA equivalent group showed a significant improvement on being upset when reminded of a stressful event, super alertness/watchfulness and total score

Courtesy, CAPT Hart, Dr. Cifu
Conclusions

- Study duplicated HBO$_2$ doses most often used clinically and recommended by advocates
- No main-effect treatment differences in post-concussion symptoms were found between sham compression, 1.5 ATA, or 2.0 ATA groups
  - Suggests anecdotal benefits are neither due to increased partial pressures of nitrogen or oxygen
- 2.0 ATA group showed only within group statistical improvement on total PCL-M
- 3 Month follow-up results are in analysis

*Courtesy, CAPT Hart, Dr. Cifu*
Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms (HOPPS)

2014: Miller S. et al; JAMA Internal Medicine

Courtesy, COL Scott Miller
Outcome Measures

• PCS has a neurologic and psychiatric component, and outcome measures are not validated
• Primary: Rivermead Post Concussion Symptom Questionnaire
• Secondary: Neurobehavioral Symptom Inventory
  • PTSD Symptoms: PCL–C (self-report questionnaire)
  • Sleep, pain, depression and anxiety symptoms
  • HRQoL measures – Satisfaction with Life Survey
  Short Form 36 Health Survey
  • Test of memory malingering (effort)
  • Neurologic: Sharpened Romberg; Smell testing
  • Psychomotor: Grooved Pegboard
  • ANAM (automated cognitive function battery)
  • Cognitive Test Battery - Stroop - CVLT-II
    - TMT - BVMT-R
    - D-KEFS - WTAR
Randomized Intervention: 1.5 ATA HBO$_2$ vs. Sham vs. Routine TBI Care

- Three arm, randomized control trial:
  1) Comparator: Routine TBI care (as defined by local MTF)

  2&3) Interventional Arms: Routine TBI care supplemented by a hyperbaric chamber procedure
  - **Active**: 1.5 ATA 100% O$_2$ for 60 min X 40 daily sessions within 10 weeks
    - Achieves plasma oxygen concentrations ~10x normal
  - **Sham**: 1.2 ATA room air, for 60 min X 40 daily sessions within 10 weeks
    - Oxygen equivalent (~2 L/min via NC)

- **Allocation**: 1:1:1 stratified by study site
- **Masking**: elaborate SOP to hide gas and pressure used; blind maintained
- **Blinding**: volunteers, medical team and assessors all blinded to assignment
Results: Demographics
1.5 ATA HBO₂ vs. Sham vs. Routine TBI Care

<table>
<thead>
<tr>
<th></th>
<th>Local Care (n=23)</th>
<th>Sham (n=25)</th>
<th>HBO₂ 1.5 (n=24)</th>
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<tbody>
<tr>
<td>Age, mean</td>
<td>30.3</td>
<td>31.4</td>
<td>32.5</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Enlisted</td>
<td>91%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Completed some college</td>
<td>65%</td>
<td>72%</td>
<td>63%</td>
</tr>
<tr>
<td># TBIs, lifetime</td>
<td>2.8</td>
<td>3.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Months since recent mTBI</td>
<td>17.2</td>
<td>26.3</td>
<td>24.9</td>
</tr>
<tr>
<td>Baseline NSI score</td>
<td>33.6</td>
<td>32.6</td>
<td>34.3</td>
</tr>
<tr>
<td>% PTSD (SCID)</td>
<td>74%</td>
<td>64%</td>
<td>54%</td>
</tr>
<tr>
<td>Baseline PCL-C score</td>
<td>51.8</td>
<td>53.5</td>
<td>48.5</td>
</tr>
<tr>
<td>TOMM Retention ≥45</td>
<td>87%</td>
<td>96%</td>
<td>92%</td>
</tr>
</tbody>
</table>

286 Calls to recruiting center
96 Not eligible/interested
140 Referred to sites for consent
72 Enrolled

37 Not eligible
29 Screening incomplete
2 Commander did not support

226 Calls to recruiting center
96 Not eligible/interested
124 Referred to sites for consent
72 Enrolled

226 Calls to recruiting center
96 Not eligible/interested
124 Referred to sites for consent
72 Enrolled

96 Not eligible/interested
140 Referred to sites for consent
72 Enrolled

2 Commander did not support
Concussion Symptoms
Neurobehavioral Symptom Inventory (NSI)

- No differences in immediate symptom responses between HBO$_2$ and sham
- Both were statistically superior to local TBI care arm, and showed maximal improvement when all 40 sessions were completed
PTSD Symptoms
PTSD Checklist- Civilian
Improvement from Baseline – ITT

- By per protocol analysis, there were no differences between HBO$_2$ and sham with reductions of 9.5 and 12.8 points, respectively

- Clinically Meaningful Change ($\geq$ 8): 20% local care, 35% HBO$_2$ and 52% sham
Exploratory Analysis
Subgroup with Baseline PTSD Scores ≥ 50

• Proponents have claimed HBO$_2$ may actually be treating PTSD, although no rational basis for a mechanism of action exists

• In this study, 39 volunteers had PCL-C scores at baseline suggestive of active PTSD
  • 84% of these carried a current DSM-4 diagnosis of PTSD
  • Responder defined as improvement of 20 points

<table>
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<tr>
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<th>Local care (n=13)</th>
<th>HBO2 (n=13)</th>
<th>Sham (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>23%</td>
<td>31%</td>
<td>54%</td>
</tr>
<tr>
<td>Non-responder</td>
<td>54%</td>
<td>62%</td>
<td>39%</td>
</tr>
</tbody>
</table>

• p value (HBO$_2$ vs. sham): 0.41
Health Related Quality of Life
Short Form 36 Health Survey
Change from Baseline – Health Concepts (ITT)

- Also no difference between HBO$_2$ and sham on Satisfaction with Life Scale with both showing modest improvement
HOPPS Summary

• In this study, standard local care offered no symptomatic improvement during the 3 month observation period

• Randomization to the chamber (either sham or HBO₂) offered statistical and in some measures clinically significant improvement over local routine TBI care
  ➢ This could explain the anecdotal findings reported

• Hyperbaric oxygen at 1.5 ATA for 40 sessions offered no statistical benefit over sham in immediate relief of PCS symptoms, PTSD symptoms, or improved quality of life

• Most likely represents placebo response to the intensive procedure
Brain Injury and Mechanisms of Action of HBO₂ for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (BIMA)
BIMA Research Study

- **Study Director:** Dr. Lin Weaver, Hyperbaric SME, LDS Hospital, Salt Lake City, UT
- **Objectives:** Validate quality of life and symptom measures, provide longitudinal assessment of brain function and anatomy before and after HBO2
- **Protocol Design:** Multi-center, double blinded, randomized control trial of proposed outcome measures in chronic mTBI (60 subjects)
  - Enrollment Sites: Cohort with chronic mTBI (SOC + sham x 40 sessions)
  - Cohort with chronic mTBI (SOC + 1.5 ATA O2 x 40 sessions)
- **Closed for enrollment:** 31 MAY 2014
  - Ft. Carson, CO/Evans Army Community Hospital
  - Joint Base Lewis-McChord, WA/Madigan Army Medical Center
  - Camp Lejeune, NC
BIMA Outcomes

• Measured at baseline, after 40 exposures, and at 6 months
• Most extensive outcomes for mTBI in the DoD
  – Neuropsychiatric – HOPPS + WHOQOL, WAIS, COWAT
  – Neurophysiologic – Rotary chair, VNG, stem cells, fundoscopy, computerized posturography, stem cells, EEG, dynamometer, physical exam with a neurologist, neuro-audiology, eye tracking and stem cell testing
  – Neuroimaging – CT angio and functional diffusion tensor MRI
• Also conducting a normative trial on “non-TBI” brains to validate outcomes – Began enrolling OCT 2013
BIMA

- Obtained FDA Investigational New Drug (IND) status
- Program Sponsor: MRMC
  - Enrollment complete, n = 71
- Ft. Carson, Colorado - Mobile multiplace hyperbaric chambers and research trailers.
Evans Army Hospital, Ft. Carson, Colorado

- CT for perfusion angiography, 320 detector: whole brain perfusion, 40 seconds, 5.7 mSv
- MRI, 3 Tesla, 32 channel coil, Functional MR equipment: anatomic MRI protocol, DTI, MR Spectroscopy, fMRI (auditory, looming)
OAC: Posturography/EEG Room
OAC: Rotational Chair
Fundus Photography

- Non-invasive & quick

Measure the angle of ocular torsion from the fovea to the center of the blind spot referenced to Earth horizontal.

- Normal orientation 2-6 degree
- Abnormal ocular torsion > 6 degree

Seen as an acute reaction to utricle damage.
OAC Sound Booth
OAC: VNG Room
Auto head rotation: Vorteq; yaw and pitch

Jacobson & Shepard (2008)
BIMA Screening & Enrollment

Initial contact to the SCC – 411
Pre-screen pass – 234
Randomized – 71
13 week f/u – 46
6 month f/u – 31
12 month f/u - 17

Goal: To have 60 with complete follow-up
Confirming the TBI Event

- In theater notes on AHLTA-T (DoD EMR)
- Reported on Post Deployment Health Assessment (PDHA)
- Directive-Type Memorandum (DTM) 09-033
  - “Mandatory Events” reported as significant acts (SIGACTS) through operational channels to the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) program office
  - Medical guidance including command directed rest and use of Military Acute Concussion Evaluation (MACE) and a CPG
MODS Applications

- 68W
- AMEDD Human Resources
- ARTS
- CMS
- e-PROFILE
- EDUCATION
- EMS
- M3PT
- MEDPROS
- MHA (PHA/DHA/Referral Tracking)
- **MWDE**
- PBCT
- RC REPORTS
- SOF
- Soldier Patient Locator
- VOLUNTEER

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<table>
<thead>
<tr>
<th>Getting Started</th>
<th>News and Events</th>
<th>Army Links</th>
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| - What is MODS? | - UM: Need access to a MODS application?  
- How do I register for MODS applications?  
- How do I register for an AKO account?  
- How do I reset my AKO account?  
- Who do I contact for help?  | - AKO - Army Knowledge Online  
- Army Medicine  
- ARNG  
- U.S. Army Home Page  
- AMEDD C & S  
- Defense Link - DoD Home Page  
- Tricare Homepage  
- DENCOM  
- MILVAX  
- USAR - U.S. Army Reserve  
- HRC Homepage  
- AMAP - Army Medical Action Plan  |

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[View All News and Events](#)
Welcome To MWDE

The Army Medical Department (AMEDD) developed the MEDPROS Web Data Entry (MWDE) module to provide a secure, online data entry portal for the posting of all immunization, medical readiness, and deployability data for all Active and Reserve components of the Army as well as DA Civilians, contractors and others. It is a powerful tool allowing those with data entry access the capability to post Immunization and Medical Readiness Information updates directly into MEDPROS as they occur. It also incorporates the feed of a Soldier’s Medical/Dental/Vision readiness status to the U.S. Army Forces Command’s (FORSCOM) Deployment and Reconstitution Tracking System’s (DARTS) automated DA Form 7425 (Sections IX Medical, X Dental, and XI Vision). For those with special access (granted separately), MWDE has built in links to the new Medical Health Assessment Module (for completion of Periodic and Deployment Health Assessments) and the eProfile Module (for the posting of both Temporary and Permanent Physical Profile PULHES and applicable Profile Codes).

Commander’s and Medical leaders at various echelons are responsible for identifying and approving those who will...
Latest Message - 2012/09/07

Changes Coming for Web Reporting, Mainframe, and MWDE

On 11 Sep 2012, MEDPROS will be moving several changes into its production programs. The changes impact Web Reporting, Mainframe, and MWDE applications and are explained in detail in the PDF file available at this link.

The Web Reporting changes include a significant reorganization of the menu layout for accessing medical readiness reports, including renaming the DHA tab to MHA and moving the PHA and NCAT reports under that menu. The Medical Readiness tab has the most significant changes with
Medical Health Assessments

Post Deployment Health Assessment for: PRICE ROBERT CHARLES

Post-Deployment Survey

Indicates Forms Completed using the DD Form 2796 April 2003 version.
Indicates Forms Completed using the DD Form 2796 January 2008 version.

Start Date | Last Updated Date | Status
---|---|---
2/3/2010 11:21:00 AM | Feb 3 2010 11:21AM | Completed

No Post-Deployment 200304 Survey on file

FOR OFFICIAL USE ONLY - Privacy Act Information
### Skin Diseases or Rashes

Other (please list):

<table>
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<tr>
<th>No</th>
<th>Yes</th>
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### Other (please list):

Describe:

<table>
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<th>No</th>
<th>Yes</th>
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</table>

9.a. During this deployment, did you experience any of the following events? (Mark all that apply)

1. Blast or explosion (IED, RPG, land mine, grenade, etc.)
2. Vehicular accident/crash (any vehicle, including aircraft)
3. Fragment wound or bullet wound above your shoulders
4. Fall
5. Other event (for example, a sports injury to your head).

Describe:

9.b. Did any of the following happen to you, or were you told happened to you, IMMEDIATELY after any of the event(s) you just noted in question 9.a.? (Mark all that apply.)

1. Lost consciousness or got "knocked out"
2. Felt dazed, confused, or "saw stars"
3. Didn’t remember the event
4. Had a concussion
5. Had a head injury

9.c. Did any of the following problems begin or get worse after the event(s) you noted in question 9.a.? (Mark all that apply.)

1. Memory problems or lapses
2. Balance problems or dizziness
3. Ringing in the ears
4. Sensitivity to bright light
5. Irritability
6. Headaches
7. Sleep problems

9.d. In the past week, have you had any of the symptoms you indicated in 9.c.? (Mark all that apply.)

1. Memory problems or lapses
2. Balance problems or dizziness
3. Ringing in the ears
4. Sensitivity to bright light
5. Irritability
6. Headaches
7. Sleep problems
DTM 09-033 Requirements

• **Specific Guidance to Commanders (Injured/HEADS/< 50 meters)**
  - H – Headaches and/or Vomiting (Yes/No)
  - E – Ears ringing (Yes/No)
  - A – Amnesia and/or altered consciousness and/or loss of consciousness (Yes/No)
  - D – Double vision and/or dizziness (Yes/No)
  - S – Something feels wrong or is not right (Yes/No)

• **Specific Guidance to providers/medics**
  - C – Cognitive score (reported with 30 point score)
  - N – Neurological exam (reported as “Green” (normal) or “Red” (abnormal))
  - S – Symptoms reported as “A” (none reported) or “B” (at least one symptom reported).
  - MACE screening evaluation can be “24/Red/B” indicating a cognitive score of 24, abnormal neurological examination, and patient reporting presence of at least one symptom
  - Dispositions developed based on “Return to Play” guidelines from the Sports Medicine concussion literature
Recruiting

• Ensure Command support
  – Warfighters and MTF
• Flyers, posters, TBI advocacy groups
• E-mail contact of Soldiers who screened positive at the SRC paid the largest dividends
• Provider to provider/ancillary staff
  – Grand rounds, monthly/quarterly training meetings, RESPECT-MIL, case managers
Hyperbaric Oxygen Treatment (HBO2) Traumatic Brain Injury Research Program

The U.S. Army Medical Materiel Development Activity is leading an effort to determine if hyperbaric oxygen is of benefit in the treatment of chronic symptoms of mild traumatic brain injury (TBI) or post-concussion syndrome (PCS).

What is a Concussion/mTBI?

- A concussion is a head injury from a hit, blow, or blast wave to the head that briefly knocks you out (loss of consciousness), or makes you feel confused or "see stars" (alteration of change in consciousness).
- Immediately or soon after the concussion, you may have disorientation, headaches, dizziness, balance difficulties, ringing in the ears, blurred vision, nausea, vomiting, irritability, temporary gaps in your memory, sleep problems, or attention and concentration problems.

Hyperbaric oxygen is defined as the administration of oxygen in a chamber at greater than sea-level atmospheric pressure in which oxygen becomes increasingly dissolved in the blood which results in greater than normal every day oxygen tension in cells and tissues in the body. There is some compelling anecdotal evidence to suggest...
HBO$_2$ for post concussive symptoms following mild TBI

**BOTTOM LINE**

- HBO$_2$ for PCS from mTBI is *investigational*
- HBO appears equivalent to breathing air at 1.2 ATA x 1 hour (sham)
- Chamber exposures may improve outcomes:
  - Placebo effects
  - Hawthorne effects
  - Therapeutic to visit the chamber daily
  - Doubtful that air at 1.2 ATA is “therapeutic” for chronic brain injury, but……If it is, mechanisms are unknown
- Complete BIMA (negotiating for annual follow up beyond 1 year) and obtain annual follow up to 2 years of DoD RCT participants
- Await *published* results from BIMA, NORMAL, LTFU, Dr. Harch’s study at LSU
- Phase III trials are not planned at this time, but BIMA results……
More Research on mTBI

Products/Devices
- Cranial nerve stimulation
- Standards for helmet

Pharmaceuticals
- FDA-approved drugs or combinations
- New pharmaceuticals under development

Alternative Therapeutics
- Nutraceuticals, such as vitamins and essential nutrients
- Nutritional approaches, such as high protein (e.g. ketogenic) diets
- Improvements in rehabilitation techniques
- Acupuncture

Objective Assessment Tools
- Blast impact sensors
- Eye tracking tools
- Biomarker blood tests
- Neuroimaging
Acknowledgements

MRMC Multicenter Study
    USAMMDA
    Walter Reed Army Institute of Research
    Evans Army Community Hosp/10th SF Group
    Naval Hospital Camp Lejeune
    Naval Hospital Camp Pendleton
    Eisenhower Army Medical Center
    LDS Hospital/University of Utah
    Denver VAMC/Center of Mental Illness Research
    Henry M. Jackson Foundation
    EmpiriStat Inc.
    OxyHeal Health Group

Dr. Lin Weaver, LDS Hospital/University of Utah
Ms. Sue Churchill, LDS Hospital/University of Utah
COL R. Scott Miller, MRMC/USHSU
LTC Austin Chheu, PMO/USAMMDA
Mr. Kyle Martin, PMO/USAMMDA
Ms. Christie Lawrence, PMO/USAMMDA
COL(R) Heidi Terrio/American Lake VA/Tacoma, WA
Dr. Paul Savage, JBLM, WA
Dr. Lisa Brenner, MIRECC, Denver VAMC
Dr. Nazanin Bahraini, MIRECC, Denver VAMC
Ms. Leah Russell, MIRECC, Denver VAMC
Ms. Maria Devore, MIRECC, Denver VAMC
Capt Laura Grogan, Evans Army Community Hospital
LCDR Virginia Skiba, Naval Hospital Camp Lejeune
CPT Corinna Bartos, Naval Hospital Camp Lejeune
LCDR Jason Gordon, Naval Hospital Camp Lejeune
CDR Jim Caviness, Naval Hospital Camp Pendleton
Questions???
References

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   Published: May 28, 2009 (v4.03: June 14, 2010).

2. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical
   Practice Guideline for Management of Concussion/Mild Traumatic Brain
   Injury (mTBI) version 1.0 2009.

3. Deputy Director of Defense: Directive-Type Memorandum (DTM) 09-033,
   “Policy Guidance for Management of Concussion/Mild Traumatic Brain
   Injury in the Deployed Setting”. June 21, 2010. Incorporating Change 3,
   November 7, 2011.