Hyperbaric Oxygen Therapy for Treatment of Persistent Post-Concussion Syndrome and Post-Traumatic Stress Disorder: Useful or Not?

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OUTLINE

• Problem of mild traumatic brain injury (mTBI)
• Potential therapeutic role for low-pressure hyperbaric oxygen therapy (HBOT) for sequelae of mTBI
• Current approval status of low-pressure HBOT for sequelae of mTBI
• OSU CAHM’s involvement in research on low-pressure HBOT for sequelae of mTBI
Learning Objectives

• Appreciate the current status of mTBI as a “problem” in the USA
• Understand the theoretical basis for therapeutic effects of HBOT and the concept of HBOT “dose”
• Be aware of the existing evidence-base for using HBOT to treat sequelae of mTBI
• Appreciate the current approval standing of HBOT for treatment of sequelae of mTBI
Problem

• mTBI ("brain concussion") is common in humans
• mTBI can have sequelae that impact injured person, family and community/society
• No effective "evidenced-based" treatment for sequelae of mTBI has been definitively identified
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Aside: A significant body of literature supports use of HBOT to treat sequelae of mTBI
What is mTBI?

• Mild, transient impairment of neurologic function due to transfer of mechanical energy to the head

• Precise pathophysiology is unknown
  o “Diffuse axonal injury” (DAI)
  o Disrupted anatomy? Physiology? or both?

• Signs and symptoms are presumed related to underlying injury to brain tissue
Acute Signs & Symptoms of mTBI

• ± loss of consciousness
• Pain (“headache” most common)
• Confusion/disorientation
• Visual and hearing disturbance
• Disturbed motor coordination and balance
• Nausea and vomiting
• Seizures
• Amnesia
Delayed Signs & Symptoms of mTBI

- Persistent or recurring headache
- Cognitive dysfunction
- Attention deficit
- Memory deficits
- Mood disturbances
- Sleep disturbances
Epidemiology of mTBI

• Varies by age and activity

• Falls and vehicle accidents are the most common cause in the U.S.

• Sports and military conflict currently high visibility due to devastating sequelae of mTBI
Natural History of mTBI

• Self-limited in most individuals to less than 3 weeks
• Persistent symptoms beyond 3 months is considered persistent post-concussion syndrome (PPCS)
• No reliable criteria to predict PPCS?
• No reliable means to prevent PPCS
Treatment of mTBI

• Because most is self-limited, “tincture-of-time” is the usual basis of treatment

• Rest and avoidance of strenuous physical or cognitive activity the regimen of choice

• Pharmacologic control of symptoms used as needed
Persistent Post-Concussion Syndrome (PPCS)

- Persistent symptoms beyond the “usual” resolution period after mTBI
- May affect 10-20% of those with new mTBI
- Syndrome may last months to years, to a lifetime
- Can follow a single mTBI episode
- Repetitive concussions may predispose to PPCS and chronic traumatic encephalopathy (CTE)
PPCS in Military Combat Veterans

- History: Recognized since WWI ("battle fatigue", "shell shock", etc.)
- Causes of injury: "Blast injury", concussive injury or combined (very likely in blast injuries)
- Many combat veterans experienced repetitive mTBIs
- The risk of CTE from repetitive incidents of mTBI in military combat veterans not known
Treatment of PPSC

- Lack of effective evidenced-based treatment
- The mainstay is drugs to attempt amelioration or control of symptoms
- Rehabilitation therapy to compensate for deficits
- No reparative ("healing") treatments
- Treatments provided are nearly universally ineffective
- Relation to current suicide epidemic?
Post-Traumatic Stress Disorder (PTSD)

- PTSD is considered a psychiatric disorder
- Caused by experiencing physical harm or threatened physical harm
- It appears to be a persistent ‘fear response’ that is not adequately controlled or extinguished
PPCS and Post-Traumatic Stress Disorder (PTSD) in Military Veterans

• Many signs and symptoms of PTSD overlap with PPCS
• Both syndromes can be caused by same event
• Likely that many combat veterans who experienced blast injury have both PPCS and PTSD (comorbidity)
• Treatment strategy for each is different
• Cognitive Behavioral Therapy (CBT) seems moderately effective treating PTSD, but not PPCS
Summary of Problem

• mTBI is common and can have persistent sequelae that impact the individual, families, and community

• No effective treatment regimen(s) for PPCS, PPCS with PTSD or CTE have been identified

• HBOT may be an effective therapy
What is HBOT?

• Definition: Exposure to combination of increased oxygen and increased ambient pressure

• Mechanism of treatment based upon principles of physics (“ideal gas laws”)
  o Increased amount of oxygen (O₂) is dissolved into body fluids

• Mechanism of action: High levels of O₂ trigger physiologic processes that heal tissue
Concept of “Dose” for HBOT

- Dose of HBOT determines therapeutic effect and toxicity
- Dose is a function of
  1. Partial pressure of $O_2$
  2. Level of increased ambient pressure
  3. Length of exposure
- $O_2$ is the most bioactive ingredient for healing
- Usual practice is to use 100% $O_2$ and adjust ambient pressure and exposure time
Approval Status of HBOT

- “Approval” status of med treatment in U.S. is based upon advertising and reimbursement
- Approving entities are the FDA and 3rd Party Payers
- FDA approval allows advertising drugs and medical equipment as “safe and effective” in interstate commerce
- 3rd Party Payers approves reimbursement to providers for treatment
Approval Status of HBOT

• HBOT is “approved” for use in treating 13 – 15 medical conditions
• HBOT is the primary treatment for a few conditions that require high pressure, e.g., decompression sickness
• HBOT is adjunctive therapy for most other conditions, i.e., necrotizing fasciitis, diabetic foot ulcer, compromised flap, chronic osteomyelitis, etc.
HBOT and mTBI with PPCS and/or PTSD

• HBOT is touted for “healing” some CNS injuries (e.g., CNS decompression injury, CO poisoning)

• *Not* currently “approved” for mTBI or sequelae of mTBI – Why?

• Evidence-base judged insufficient to support therapeutic effect by approving entities and some medical authorities
Evidence-Base for HBOT

• A substantial body of literature exists that supports using HBOT for mTBI sequelae

• Most studies were not the “gold standard” for the highest level of evidence, i.e., randomized, prospective, double-blind, placebo/sham-controlled

• The literature prior to about 2005 consisted of
  o Animal models
  o Case reports, case series, cohort studies
  o Studies of other CNS injuries and conditions
  o More recently, PRDBSC studies published in lower-tier journals
Evidence-Base for HBOT

- Department of Defense (DOD) conducted a series of prospective, randomized, sham-controlled studies widely interpreted as “non-supportive” of significant effect of HBOT for PPCS with and without PTSD
- All were PRDBSC studies and well executed
- Each used different dose of HBOT and different sham controls
- Statistically significant improvements in dependent variables in both experimental and sham treated groups
Evidence-Base for HBOT

• Advocates for HBOT argue that the DOD studies were supportive of HBOT because both study groups improved
• Advocates believe that the sham conditions used actually constitute a lower dose of HBOT
• Advocates believe there is no valid sham possible for the combination of pressure and oxygen and even low pressure with 21% oxygen have positive effects
Evidence-Base for HBOT

• Two recent studies from Israeli researchers using a “stepped wedge” study design appear to give supportive evidence for HBOT stimulating neuroplasticity in a variety of CNS injuries and in individuals with PPCS from blast and concussive injuries.

• Advocates for HBOT believe that this control design is the best that can be done for the combination of pressure and oxygen.
Summary: Evidence-Base for HBOT

• HBOT community is currently divided
  o Advocates for the low-pressure HBOT protocol believe that an adequate sham for pressure and oxygen is not possible
  o “Gold-standard” advocates believe that the sham treatments used in the DOD studies were adequate and HBOT is not effective for mTBI sequelae

• Unlikely schism will be healed until a sham that is acceptable to both groups is used
OSU-CAHM Experience With Low-pressure HBOT for Treating mTBI and/or PTSD

- OSU CAHM was a participating site in NBIRRR study
  - Multi-center observational study
  - OSU CAHM recruited and treated the largest number of volunteers
  - Results not published yet (peer-reviewers not supportive)
IHMF National Brain Injury Rescue and Rehabilitation (NBIRR) Study
OSU-CHS Experience With Low-pressure HBOT for Treating mTBI and/or PTSD

• Appeared to work for well for mTBI with or without PTSD for individuals completed 40 treatments to 80 treatments
• Seemed to work best for younger individuals and those with shorter interval from injury event
• Did not have much effect for more severe head injuries
• Safe – only significant injury was possible exacerbation of previously undocumented perilymphatic fistula (PLF)
• Only case of “pure” PTSD (no head trauma) responded remarkably well
Conclusions

• There is a promising evidence base for using the low-pressure HBOT protocol to treat mTBI with PPCS and/or PTSD
• In the era of “evidenced-base medical practice” HBOT probably will not get approved (or rejected) until a “gold standard” study using a sham every one accepts is completed
References


