Supplementary Online Content

Miller RS, Weaver LK, Bahraini N, et al; HOPPS Trial Team. Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms: A Randomized Clinical Trial. Published online November 17, 2014. *JAMA Intern Med*. doi:10.1001/jamainternmed.2014.5479

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Volunteers must have history of at least one mTBI with persistent symptoms that meets all the following criteria: • Brain injury that occurred more than 4 months prior to enrollment, with the most recent injury occurring no earlier than October 7,2001. • Most recent traumatic brain injury occurred while serving on active duty, and while deployed to the US Central Command (USCENTCOM). • Most recent traumatic brain injury was caused by blast exposure or blunt trauma. • Most recent traumatic brain injury resulted in at least one of the following: a period of loss of or a decreased level of consciousness (up to 30 minutes); a loss of memory for events immediately before or after the injury (up to 24 hours); or alteration in mental state at the time of the injury (becoming dazed or confused). Volunteers must also meet all the following criteria: • 18-65 years old at the time of study enrollment. • A TRICARE beneficiary at the time of consent and during study participation. • Has current complaints of brain injury symptoms such as headache, dizziness, or cognitive or affective problems that score at least 3 post-concussive symptoms as assessed by the OSU TBI-ID interview • Has received current local care pharmacologic and non-pharmacologic interventions for TBI and any concomitant PTSD with no significant change in therapy for at least 1 month • Willing and committed to comply with the research protocol and complete all outcome measures. • Able to self-consent. • Able to speak and read English, as primary language. • Able to participate in all outcome measures. • Able to equalize middle ear pressure.	• History of brain injury of moderate or severe degree: duration of loss of consciousness at the time of injury greater than 30 minutes, or duration of post-traumatic amnesia greater than 24 hours, or brain injury of a penetrating etiology. • History of brain injury not of traumatic etiology, such as a stroke or drug-induced coma. • Prior treatment with HBO_2. • Hyperbaric chamber inside attendant, professional (paid) underwater diver (commercial, operational/ military, instructor), or technical diver. • Pregnancy, women who plan to become pregnant during the study period, women who do not agree to practice an acceptable form of birth control during the study period, or women who are breastfeeding; • Those who are unable to participate fully in outcome assessments (Blind in one or both eyes; Deaf in one or both ears; or Ambulation with assistive devices • Pre-existing diagnosis of a psychotic disorder(s): schizophrenia, dissociative disorder, and bipolar disease. • Verifiable degenerative mental disease (e.g., Alzheimer's disease, multiple sclerosis, senile dementia). • Epilepsy or seizure disorder requiring anticonvulsants. • Active malignancy, prior malignancy (except basal cell carcinoma) within the last 5 years. • Presence of chronic debilitating disease (e.g., end-stage renal disease, end-stage liver disease, all types of diabetes with or without sequelae). • Documented clinically significant uncorrected anemia • Documented sickle cell disease. • History of therapeutic ionizing radiation to the head. • Verifiable diagnosis of learning disability. • Positive urine test for an illicit substance(s). • Any condition or use of prescribed medication (lithium, cisplatin, doxorubicin, or bleomycin) in which receipt of HBO_2 would impact the safety of the individual. • Anticipated administrative separation, prolonged TAD/TDY or deployment within 3 months after randomization • Claustrophobia (unwilling or unable to enter

	hyperbaric chamber). • Inability to protect airway or requires frequent suctioning; presence of tracheostomy • Heart failure with ejection fraction < 50% (due to increased risk for precipitating acute lung edema during exposure to HBO_2). • Emphysema, chronic bronchitis, or bullous lung disease (due to risk for pulmonary barotrauma during hyperbaric decompression). • Diabetes (relative contraindication related to risk of hypoglycemia). • Presence of implanted device (e.g., cardiac defibrillator, intrathecal drug delivery device, cochlear implant) that poses increased risk to subject during hyperbaric exposure.

eMethods 2. Hyperbaric Oxygen and Sham Administration Procedures

Multiplace hyperbaric chambers were used for all compressions. Compressions were administered daily on work days. Recognizing the many demands on time due to other medical appointments and job requirements, volunteers were required to complete 40 hyperbaric compressions with a 10 week window period.

Test Procedure: Hyperbaric Oxygen at 1.5 Atmosphere Absolute (ATA)
The chamber was compressed with air to 1.5 ATA. Once the chamber reached 1.5 ATA, the subjects donned a hood and breathed 100% oxygen (USP oxygen 99-100%). Hoods were supplied with oxygen with flows of at least 30 liters per minute and overboard dumping of excess gas. The duration of the hyperbaric oxygen exposures was be 60 minutes (±2 minutes), timed from when the chamber hatch or door closes, and ending when the chamber hatch or door opens ("door-to-door" time equals 60 minutes). The hood remained in place until the chamber begins decompression to atmospheric pressure, at which time the gas flow to the hoods will be terminated and the hoods may be removed.

The total intervention exposure time at final pressure was 50 minutes (±2 minutes). The time to compress to the intervention pressure (1.5 ATA) was 5 minutes (±1 minute). The time to decompress from the study pressure was 5 minutes (±1 minute).

Sham Procedure: Room Air at 1.2 Atmosphere Absolute (ATA)
The chamber was compressed with air to 1.2 ATA to simulate the hyperbaric oxygen procedure. At this pressure, the subjects have to equalize middle ear pressure; however, this oxygen dose should have no therapeutic benefit (equivalent of an equivalent inhaled oxygen concentration of 25%). A few minutes after the chamber is compressed to 1.2 ATA (to equal compression time of the active groups), the subjects donned a hood and breathe USP medical grade air (approximately 79% nitrogen/21% oxygen). Hoods were supplied with medical grade air with flows of at least 30 liters per minute and overboard dumping of excess gas.

The total intervention exposure time at final pressure was 50 minutes (±2 minutes). The time to compress to the intervention pressure (1.2 ATA) was 5 minutes (±1 minute). The time to decompress from the study pressure was 5 minutes (±1 minute).

Additional Steps to Ensure Blinding
Oxygen is odorless and colorless, so only the pressurization variability or inadvertent disclosure by the chamber technician staff could unblind a volunteer. Only the hyperbaric chamber technicians opened randomization envelopes and were aware of the group to which individuals were randomized. Only they knew which compression protocol was being followed on a given compression. The technicians maintained a separate work area from the study coordinators or physicians supervising a compression. The dive console was hidden by a curtain so gauges were not visible to other staff, and the interior chamber gauges were covered. Additionally, extra chamber venting cycles were run with the sham arm to match hyperbaric sessions.

eMethods 3. Patient Reported Outcomes and Neuropsychological Testing Battery

Screening and Assessment Tools

- Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID)
- Structured Clinical Interview for DSM-IV (SCID) PTSD Module
- University of Washington Risk Assessment Protocol (UWRAP)
- Simple Visual Acuity (SVA)
- Test of Memory Malingering (TOMM)

Primary Outcome Assessment Tools – Concussion Symptoms

- Neurobehavioral Symptom Inventory (NSI)
- Rivermead Post-Concussion Symptoms Questionnaire (RPQ)

Secondary Outcome Assessment Tools

Patient Reported Outcomes

- Post-Traumatic Stress Disorder Checklist-Civilian Version (PCL-C)
- Center for Epidemiological Studies-Depression Scale (CES-D)
- Beck Anxiety Inventory (BAI)
- Alcohol Use Disorders Identification Test Consumption (AUDIT-C)
- Pittsburgh Sleep Quality Index (PSQI)
- McGill Pain Questionnaire (MPQ-SF)
- Short Form 36 Health Survey (SF-36)
- Satisfaction with Life Scale (SWLS)

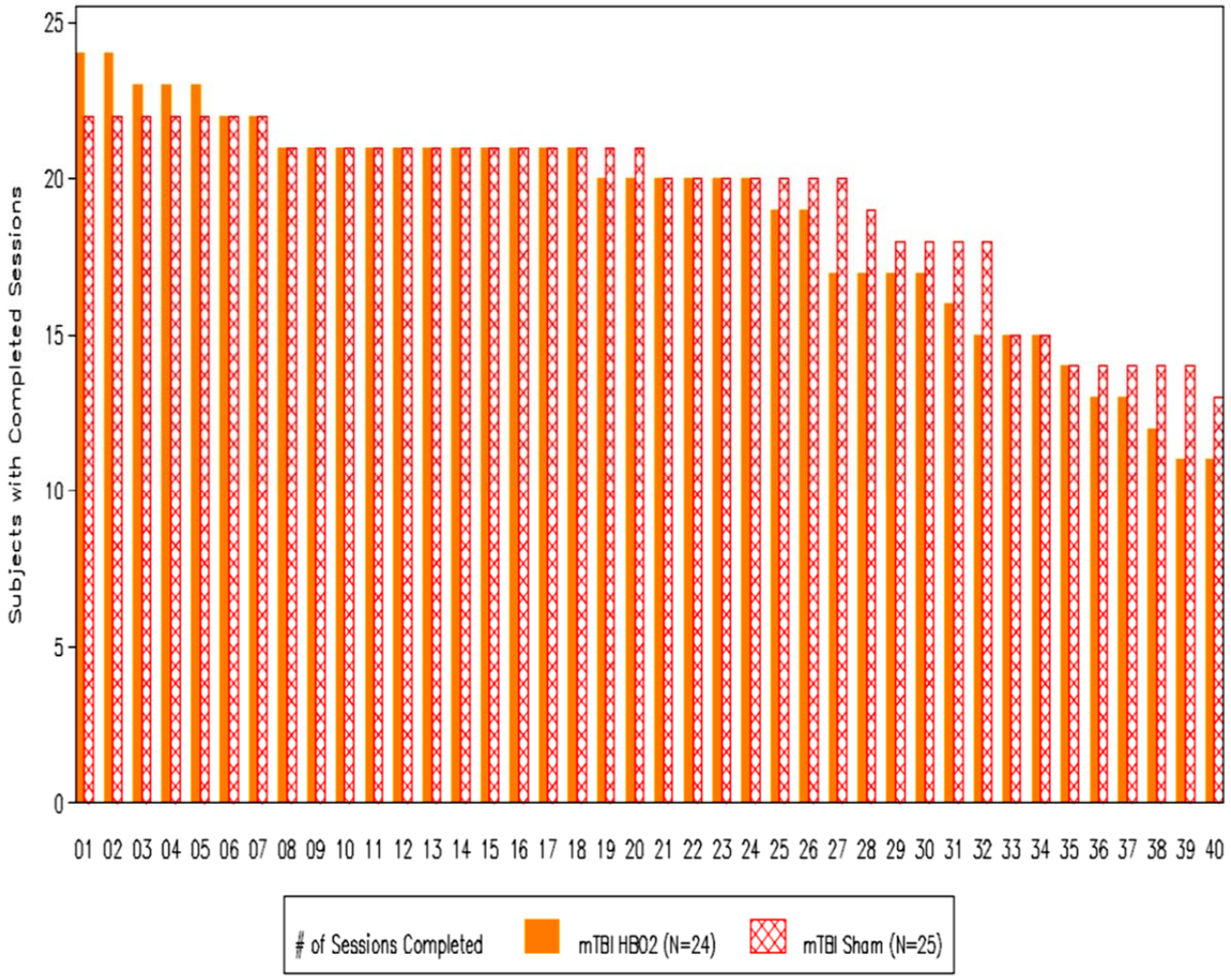
Neuropsychologic Testing

- Automated Neuropsychological Assessment Metrics (ANAM4 TBI-MIL)
- California Verbal Learning Test, Second Edition (CVLT-II)
- Trail Making Test (parts A and B) (TMT)
- Brief VisuoSpatial Memory Test Revised (BVMT-R)
- Stroop Color and Word Test (STROOP)
- Grooved Pegboard
- Delis-Kaplan Executive Function System
  Verbal and Category Fluency Tests (D-KEFS)
- Weschler Test of Adult Reading (WTAR)

Neurologic Testing

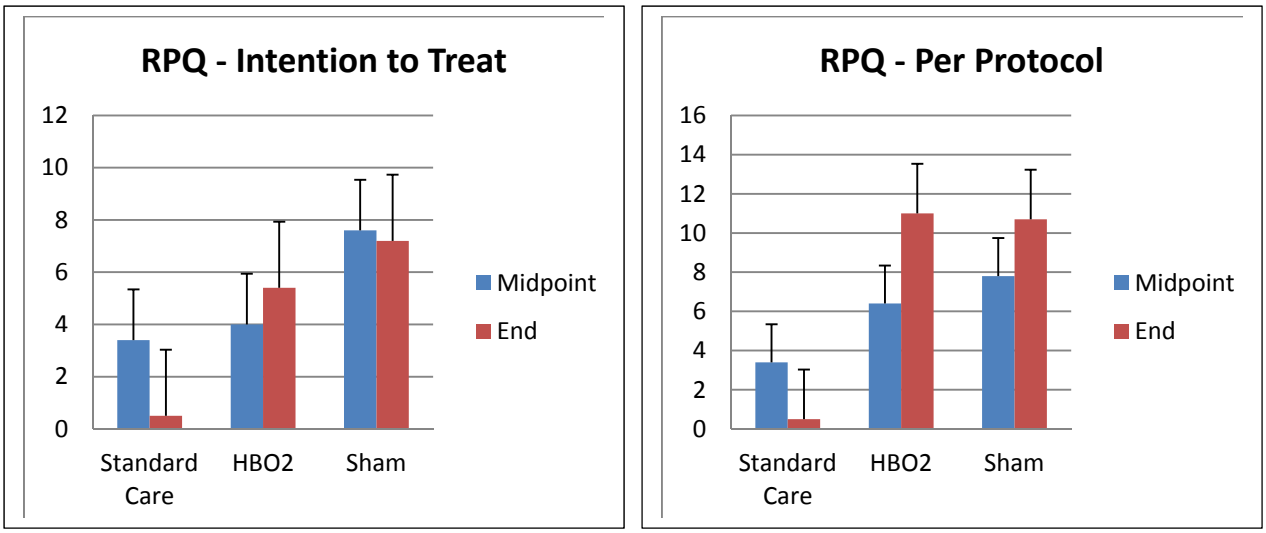
- Sharpened Romberg (SRT)
- Brief Smell Identification Test (B-SIT)

eFigure 1. Histogram of the Number of Hyperbaric Chamber Sessions Completed Within Study Period

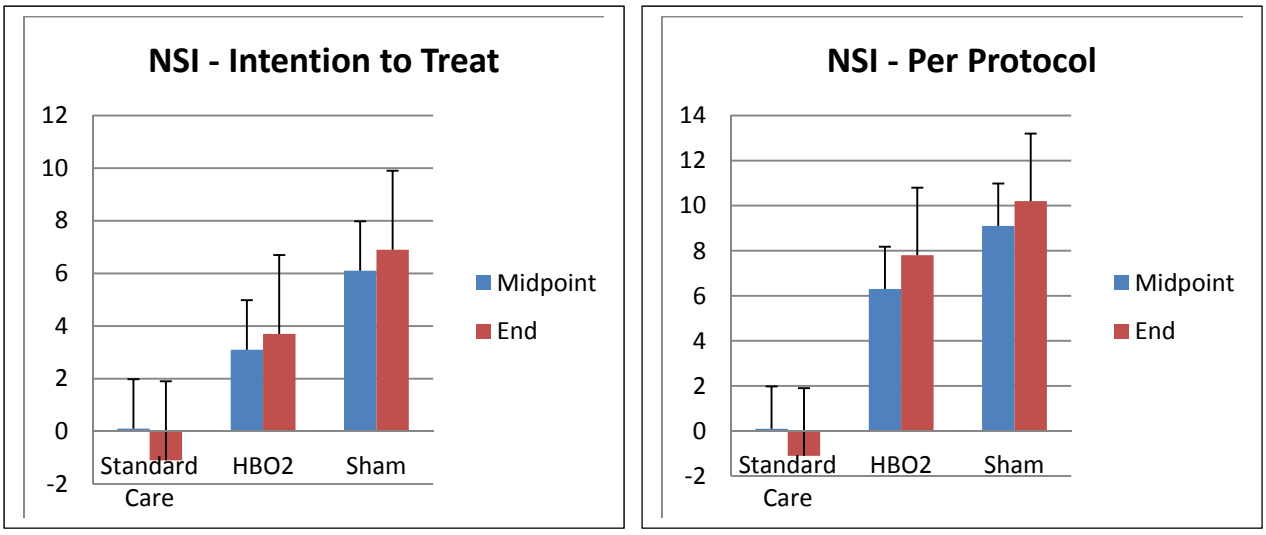


eFigure2. Comparison of Change From Baseline Scores for Postconcussion Symptoms at the Midpoint (20 Sessions) and the End of the Intervention

a. Rivermead Post Concussion Symptoms Questionnaire (RPQ) Total Scores after 20 and 40 sessions



b. Neurobehavioral Symptom Inventory (NSI) Total Scores after 20 and 40 sessions



Note: Errors bars represent SE for the total score

eTable. Summary of Chamber Intervention–Related Adverse Events

	Intervention	
AE Severity	**Hyperbaric Oxygen 1.5 ATA x 60 mins (n=24)**	**Room Air at 1.2 ATA (Sham) x 60 mins (n=23)**
Mild	Middle ear pain (1) Tooth pain (1) Inner ear barotrauma (2) Onset migraine headache (1) Increase frequency and intensity of headaches (1)‡ Transient worsening of myopia (1)*	Sinus pain (3) Middle ear pain (1) Change in headache frequency (1) Claustrophobia/anxiety (1)‡
Moderate	Inner ear barotrauma, TEED Grade 2 (1)	None
Severe	None	None
Serious (SAE)	None	None

AEs were attributed to chamber pressurization, except as noted with an asterisk, which was attributed to oxygen.

‡ These AEs were associated with a voluntary discontinuation of chamber sessions.