Research Article

Hyperbaric oxygen for post-concussive symptoms in United States military service members: a randomized clinical trial

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† *Dr. Orrison passed away during the peer review process for this paper. We are grateful for his participation in this important project.*

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ABSTRACT

Background: In prior military randomized trials, participants with persistent symptoms after mild traumatic brain injury (TBI) reported improvement regardless of receiving hyperbaric oxygen (HBO_2) or sham intervention. This study's objectives were to identify outcomes for future efficacy trials and describe changes by intervention.

Methods: This Phase II, randomized, double-blind, sham-controlled trial enrolled military personnel with mild TBI and persistent post-concussive symptoms. Participants were randomized to receive 40 HBO_2 (1.5 atmospheres absolute (ATA), >99% oxygen, 60 minutes) or sham chamber sessions (1.2 ATA, room air, 60 minutes) over 12 weeks. Participants and evaluators were blinded to allocation. Outcomes assessed at baseline, 13 weeks and six months included symptoms, quality of life, neuropsychological, neurological, electroencephalography, sleep, auditory, vestibular, autonomic, visual, neuroimaging, and laboratory testing. Participants completed 12-month questionnaires. Intention-to-treat results are reported.

Results: From 9/11/2012 to 5/19/2014, 71 randomized participants received HBO_2 (n=36) or sham (n=35). At baseline, 35 participants (49%) met post-traumatic stress disorder (PTSD) criteria. By the Neurobehavioral Symptom Inventory, the HBO_2 group had improved 13-week scores (mean change -3.6 points, P=0.03) compared to sham (+3.9 points). In participants with PTSD, change with HBO_2 was more pronounced (-8.6 vs. +4.8 points with sham, P=0.02). PTSD symptoms also improved in the HBO_2 group, and more so in the subgroup with PTSD. Improvements regressed at six and 12 months. Hyperbaric oxygen improved some cognitive processing speed and sleep measures. Participants with PTSD receiving HBO_2 had improved functional balance and reduced vestibular complaints at 13 weeks.

Conclusions: By 13 weeks, HBO_2 improved post-concussive and PTSD symptoms, cognitive processing speed, sleep quality, and balance function, most dramatically in those with PTSD. Changes did not persist beyond six months. Several outcomes appeared sensitive to change; additional studies are warranted.

ABBREVIATIONS

TBI: traumatic brain injury
PTSD: post-traumatic stress disorder
HBO_2: hyperbaric oxygen
US: United States
NSI: Neurobehavioral Symptom Inventory
BIMA: Brain Injury and Mechanisms of Action of HBO_2 for persistent post-concussive symptoms after mild TBI study

STUDY IDENTIFIERS: BIMA study; www.ClinicalTrials.gov: NCT01611194

INTRODUCTION

Disability from traumatic brain injury (TBI) affects millions in the United States (U.S.) [1], and combat military personnel have increased risk for TBI [2] and persistent post-concussive symptoms [3,4]. The TBI process [5] and multi-domain expression complicate therapy, but case series and unblinded randomized trials suggest hyperbaric oxygen (HBO_2) may provide benefit [6-8]. During HBO_2, a patient is placed inside a chamber and breathes >99% oxygen at increased atmospheric pressure, raising blood/tissue oxygen tension, with many physiological effects [8].

The U.S. military sponsored several randomized, sham-controlled trials of HBO_2 for post-concussive symptoms [9]. Although these trials were underpowered for efficacy, participants receiving either sham or HBO_2 reported symptom improvement [10-12]. This current study, BIMA (Brain Injury and Mechanisms of Action of HBO_2 for persistent post-concussive symptoms after mild TBI), incorporated comprehensive assessments and one-year follow-up [13]. Primary objectives were to identify outcomes for possible future efficacy trials and describe changes by intervention. A separate non-intervention study of healthy volunteers provides context for BIMA results [9].

METHODS

BIMA was a Phase II, exploratory, randomized, double-blind, sham-controlled trial of HBO_2 for military personnel with post-concussive symptoms three months to five years after mild TBI. BIMA was conducted under an Investigational New Drug application and approved by the U.S. Army Medical Research and Materiel Command institutional review board. This study and the companion study of healthy volunteers were registered at *www.clinicaltrials.gov* (NCT01611194, NCT01925963).

Participants

Participants were recruited in the United States from Joint Base Lewis-McChord, Washington, Fort Carson, Colorado, and Camp Lejeune, North Carolina. Eligible active duty personnel or veterans were 18-65 years old with symptoms from ≥1 mild TBI (by structured interview [14] and medical records) occurring on active duty, with loss of consciousness ≤30 minutes, altered consciousness ≤24 hours, or post-traumatic amnesia ≤1 day [15]. Consistent with post-concussive syndrome, ≥3 persistent symptoms were required for enrollment [13-15]. Exclusions included moderate/severe TBI, non-traumatic or penetrating brain injuries, or confounds of outcome measures or blinding [13]. Participants were required to be stable on medications/interventions for ≥30 days before enrollment.

Randomization

Potential participants telephoned a centralized screening location; written informed consent and eligibility assessments were conducted at local military sites. Participants were informed they should not expect direct benefit from study participation. Active duty participants received command permission for enrollment, but assessment results were not provided to the command or military medical evaluation boards. Participants were assigned to HBO_2 or sham via computer using 1:1 randomization (by the Emmes Corporation) with random permuted block sizes 4/6, stratified by site, time since most recent TBI (≤1 year, >1-5 years), and morning/afternoon schedule preference.

Procedures

Daily one-hour sessions were provided Monday-Friday in multiplace hyperbaric chambers at recruitment sites. Participants were to receive 40 HBO_2 (>99% oxygen, 1.5 atmospheres absolute (ATA)) or sham (air, 1.2 ATA) sessions over 12 weeks to accommodate command and participant schedules. The sham pressure was below the threshold for clinical HBO_2 therapy but required middle ear equalization to preserve the blind. Only certified hyperbaric technologists had access to chamber records and controls/gauges, to ensure participants and study staff remained blinded.

Outcomes

Participants were evaluated at a central assessment center (Colorado Springs, Colorado) at baseline, 13 weeks (one week post-intervention period), and six months (Figure 1). Participants completed online/telephone questionnaires at 12 months [13].

Demographics, history, and physical examination were recorded at baseline. The Structured Clinical Interview for DSM-IV PTSD module [16] was administered to diagnose post-traumatic stress disorder (PTSD) at enrollment. Medications, therapies and

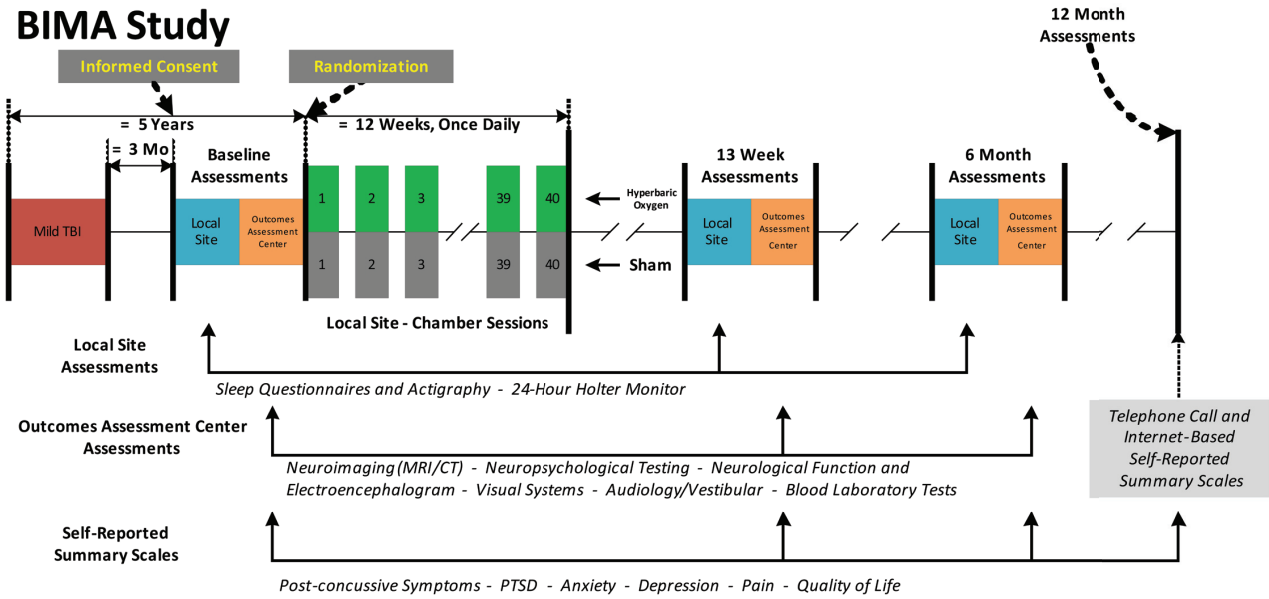

FIGURE 1. Study design

Participants were able to tolerate the extensive assessment battery, which occurred three times during the study and consisted of more than 20 hours of direct assessment and testing, including 2.5-hour magnetic resonance imaging without sedation, at each interval.

adverse events were documented at each study visit. At 13 weeks, participants specified which intervention they believed they received.

Outcome assessments approximated prior military studies and included symptoms, quality of life, and neuropsychological testing. Questionnaires were self-administered in private rooms, with study personnel available for questions. Neurological, electroencephalography, sleep, auditory/vestibular, electrocardiography, vision, neuroimaging, and laboratory measures were included to explore potential intervention-linked mechanisms and increase knowledge about TBI. Methods and baseline data for most domains are previously published [13,17-22]. Trained, certified examiners and technicians performed neuropsychological and functional evaluations, electroencephalography, electrocardiography and neuroimaging. Physician and doctoral experts interpreted data and performed neurological examinations and auditory/vestibular testing. A full list of assessments and references for these are provided in Table 1.

After trial commencement, protocol amendments allowed verbal consent before telephone screening and veteran participation.

Statistical analysis

Up to 72 participants were randomized so 60 would complete ≥20 chamber sessions with 13-week follow-up. Intention-to-treat results are presented.

Tests of baseline and change from baseline differences between intervention groups and between and within subgroups were evaluated. Researchers used t-tests for continuous and Chi-square tests for discrete outcomes. Tests included summary and individual outcomes for 11 major domains and subgroups of PTSD, age, and trauma. Presented results focus on outcomes similar to prior studies [10-12].

Linear mixed models and generalized estimating equations evaluated differences over time between intervention groups. The modeling strategy was specified a priori in the statistical analysis plan; models include effects for time, intervention, time-by-intervention interaction, and design factors (e.g., study site, time since injury, chamber session preference). Continuous outcomes were modeled with response beginning at the 13-week time point, and models were adjusted for baseline outcome value. A baseline value-by-intervention group effect was considered in the model selection process to account for potential baseline differences between intervention groups. For longitudinal models, baseline age, bioavailable Vitamin

TABLE 1. Outcome assessment schedule

ASSESSMENT DOMAIN	Baseline	13 Weeks	6 Months	12 Months
Post-concussive symptoms and quality of life				
Ohio State University Traumatic Brain Injury Identification [14]	Site	Site	Site	Phone
Structured Clinical Interview for DSM-IV, PTSD module [16]	Central	Central	Central	
Neurobehavioral Symptom Inventory [37]	Central	Central	Central	Phone/web
Rivermead Post-Concussive Symptom Questionnaire [38]	Central	Central	Central	Phone/web
Post-Traumatic Stress Disorder Checklist - Civilian Version [39]	Central	Central	Central	Phone/web
Center for Epidemiological Studies - Depression Scale [40]	Central	Central	Central	Phone/web
Beck Anxiety Inventory [41]	Central	Central	Central	Phone/web
Alcohol Use Disorders Identification Test – Consumption [42]	Central	Central	Central	Phone/web
RAND 36 Health Survey [43]	Central	Central	Central	Phone/web
World Health Organization Quality of Life Questionnaire [44]	Central	Central	Central	Phone/web
Satisfaction with Life Scale [45]	Central	Central	Central	Phone/web
McGill Pain Questionnaire [46]	Central	Central	Central	Phone/web
Patient Global Impression of Change [47]		Central	Central	
Neuropsychological testing				
Automated Neuropsychological Assessment Metrics [48]	Central	Central	Central	
California Verbal Learning Test – II [49]	Central	Central	Central	
	Standard form	Alternate form	Standard form	
Brief Visuospatial Memory Test – Revised [50]	Central Form 1	Central Form 2	Central Form 3	
Test of Memory Malingering [51]	Central	Central	Central	
Wechsler Adult Intelligence Scale – IV, digit span and processing speed [52]	Central	Central	Central	
Wechsler Test of Adult Reading [53]	Central	Central	Central	
Stroop color and word test [54]	Central	Central	Central	
Controlled oral word association test [55]	Central	Central	Central	
Trailmaking test – parts A and B [56]	Central	Central	Central	
Grooved pegboard [57]	Central	Central	Central	
State-Trait Anger Expression Inventory – 2 [58]				
Neurological and functional evaluation [17,18]	Site	Site	Site	
Neurological examination [17]	Central	Central	Central	
Romberg and Sharpened Romberg tests [59]	Central	Central	Central	
Brief Smell Identification Test [60]	Central	Central	Central	
Berg Balance Scale (BBS) [61]	Central	Central	Central	
Grip strength (dynamometer) [62] and 6-minute walk test [63]	Central	Central	Central	
Electroencephalography [18]	Central	Central	Central	
Sleep Assessments [20]				
STOP-Bang Questionnaire [64]	Site	Site	Site	
Pittsburgh Sleep Quality Index (PSQI) [65]	Site	Site	Site	
Actigraphy [66,67]	Site/Central	Site/Central	Site/Central	
Sleep diary [68]	Central	Central	Central	
Restless legs questionnaire [69]	Site	Site	Site	
Cataplexy questionnaire [70]	Site	Site	Site	

TABLE 1. Outcome assessment schedule

ASSESSMENT DOMAIN	Baseline	13 Weeks	6 Months	12 Months
Auditory and vestibular systems [21]				
Vestibular symptoms questionnaire [21]	Central	Central	Central	
Peripheral and central auditory examination [21]	Central	Central	Central	
Videonystagmography [71]	Central	Central	Central	
Computerized dynamic posturography [72]	Central	Central	Central	
Rotational vestibular test, oculomotor examination [72]	Central	Central	Central	
VORTEQ™ active head rotation test [73]	Central	Central	Central	
Cervical and ocular vestibular evoked myogenic potentials (cVEMP, oVEMP) [74]	Central	Central	Central	
Autonomic function				
24-hour Holter monitoring and motion detection [19]	Site	Site	Site	
Visual system				
Refractive error	Central	Central	Central	
Dynamic visual acuity [75]	Central	Central	Central	
Retinal fundoscopy [76]	Central	Central	Central	
Dynavision [77]	Central	Central	Central	
Eye tracking system [78]	Central	Central	Central	
Neuroimaging				
Magnetic resonance imaging (MRI) without gadolinium Arterial spin labeling, diffusion tensor imaging, proton magnetic resonance spectroscopy, functional MRI: resting state, auditory, looming protocol	Central	Central	Central	
Computed tomography angiography with and without contrast	Central	Central	Central	
Laboratory testing				
Illicit drug screening	Site	Site	Site	
Pregnancy screening	Site/Central	Site/Central	Site/Central	
Flow cytometry	Central	Central	Central	
Biological material storage	Central	Central	Central	

D, and PTSD diagnosis were considered for inclusion using stepwise selection. To evaluate the impact of baseline characteristic factors on the size and direction of the intervention effects, post-hoc longitudinal models of post-concussive and PTSD symptoms were generated with adjustment for baseline characteristic distributions found to be different between the intervention groups.

Hypothesis testing was two-sided, α=0.05, unadjusted for multiple comparisons. To aid interpretation of cross-domain results and decrease the impact of multiple testing, a modified generalized least squares approach [23] estimated global effect, adjusting for correlations, across symptoms, quality of life, neuropsychological, neurological, sleep, and auditory/vestibular outcomes.

RESULTS

From September 11, 2012, to May 19, 2014, BIMA randomized 71 participants (Figure 2); 36 received HBO_2 and 35 sham. Twenty-nine (81%) HBO_2 and 30 (86%) sham participants completed 40 sessions. One sham participant missed 13-week follow-up, and one in each group missed six-month follow-up. Three sham participants withdrew before 12-month follow-up.

Mean age was 33 years (range 21-53). Participants reported a mean 3.6 mild TBIs (lifetime) and were 26 months from their most recent TBI. Twenty-three (32%) reported blast injuries only, and 35 (49%) met PTSD criteria [16] at enrollment. Medication, supplement and therapy use was frequently reported and did not significantly change during the study for either group.

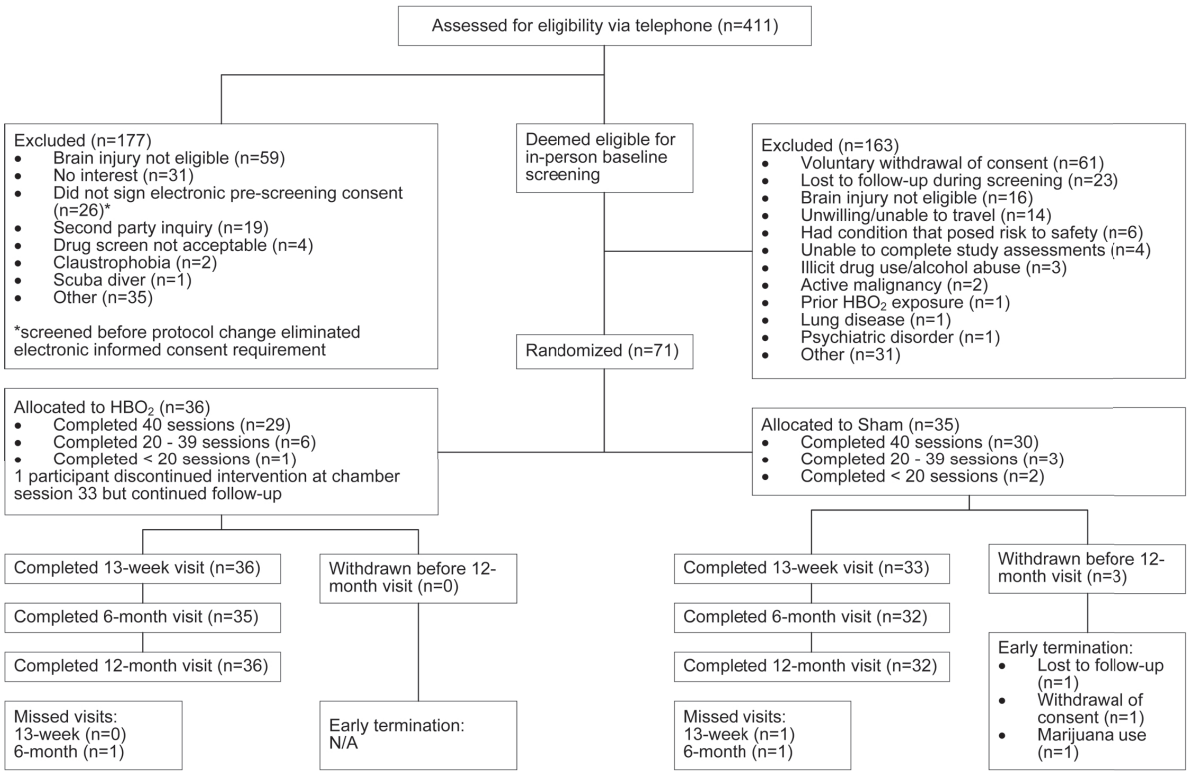

FIGURE 2. CONSORT diagram

Intent-to-treat analysis included all randomized participants (n=71).

The HBO_2 group was older, with more combat deployments, worse anger control, and more frequent diffuse/traumatic axonal injury by neuroimaging; other characteristics were balanced (Table 2). Despite these differences potentially suggesting worse brain injury in the HBO_2 group, most baseline post-concussive and PTSD symptom scores were similar between intervention groups, except the Rivermead Post-Concussion Symptom Questionnaire (RPQ) total, RPQ-13, and PTSD Checklist-Civilian Version hyperarousal score, which were worse in the HBO_2 group (Tables 3, 4).

In univariate and longitudinal testing, the RPQ-3 domain (headaches, dizziness, nausea) [24] improved in the HBO_2 group at 13 weeks compared to sham (mean change difference -1.5, 95% confidence interval (CI) [-2.7, -0.3], P=0.01). Neurobehavioral Symptom Inventory (NSI) total (Figure 3), and affective domain change scores favored HBO_2 in univariate testing only. Improvement with HBO_2 was greater in participants with PTSD. Participants without PTSD had no significant changes with either intervention, but change scores favored HBO_2.

At six and 12 months, differences between groups diminished. Symptoms of PTSD (by PTSD Checklist total score) (Table 3, Figure 3) improved with HBO_2 compared to sham at 13 weeks, confirmed by longitudinal modeling (P=0.04). Improvements at six months were not significant. Post-concussive and PTSD symptoms in both groups were worse at 12 months than at baseline (not statistically significant).

At 13 weeks, the State-Trait Anger Expression Inventory (Table 4) Anger Expression Index and Anger Control-In domains improved in the HBO_2 group by univariate (P=0.01, P=0.005, respectively) and longitudinal modeling. Other subscores favored HBO_2 (not statistically significant).

By the Patient Global Impression of Change, more HBO_2 participants (19/36) reported benefit (score ≥5) than sham participants (10/33) at 13 weeks and six months (19 HBO_2 vs. five sham participants).

On other neuropsychological measures (Table 5), 13-week change scores improved with HBO_2 compared to sham (39/43 measures, Figure 4), but many did not reach statistical significance. Sham was never signifi-

TABLE 2. Participant baseline characteristics [a]

Characteristics	HBO_2 Group (N=36)	Sham Group (N=35)	P-value	BIMA Total (N=71)
Age, years	34.8±8.3	30.8±5.5	0.02	32.8±7.3
Male sex, N (%)36 (100%)	34 (97%)	0.49	70 (99%)	
Body mass index	29.1±3.9	29.5±5.0	0.72	29.3±4.4
Education, N (%)				
High school diploma	7 (19%)	6 (17%)	0.80	13 (18%)
Some college or more	29 (81%)	29 (83%)		58 (82%)
Military status, N (%)				
Active duty	35 (97%)	33 (94%)	0.61	68 (96%)
Veteran	1 (3%)	2 (6%)		3 (4%)
Time from most recent qualifying mild TBI, mo	25.6±17.1	25.5±15.4	0.97	25.6±16.2
Lifetime mild TBI injuries	3.6±3.2	3.7±2.3	0.88	3.6±2.8
Mild TBI injury type, N (%)				
Blast injuries only	15 (42%)	8 (23%)	0.20	23 (32%)
Blunt force head injuries only	7 (19%)	7 (20%)		14 (20%)
Combination of blast and blunt force injuries	14 (39%)	20 (57%)		34 (48%)
Post-concussive symptoms [14], N (%)				
Headache	33 (92%)	32 (91%)	>0.99	65 (92%)
Dizziness/balance problems	31 (86%)	26 (74%)	0.21	57 (80%)
Blurred vision	14 (39%)	15 (43%)	0.73	29 (41%)
Tiredness/fatigue or sleep problems	33 (92%)	35 (100%)	0.24	68 (96%)
Remembering things or solving problems	35 (97%)	33 (94%)	0.61	68 (96%)
Managing stress or emotional upsets	28 (78%)	27 (77%)	0.95	55 (77%)
Controlling temper/irritability	32 (89%)	27 (77%)	0.19	59 (83%)
Ringing in the ears	29 (81%)	26 (74%)	0.53	55 (77%)
PTSD diagnosis [16], N (%)	18 (50%)	17 (49%)	0.90	35 (49%)
Combat deployments	3.4±2.8	2.2±1.7	0.04	2.8±2.4
Alcohol use disorder, N (%)	11 (31%)	8 (23%)	0.46	19 (27%)
Number of medications reported	8.6±5.2	6.6±3.6	0.07	7.6±4.7
Antidepressants, N (%)	22 (61%)	17 (49%)	0.29	39 (55%)
Hypnotics and sedatives, N (%)	15 (42%)	14 (40%)	0.89	29 (41%)
Antimigraine medications, N (%)	16 (44%)	14 (40%)	0.70	30 (42%)
Narcotic pain control, N (%)	9 (25%)	6 (17%)	0.42	15 (21%)
Non-narcotic pain control, N (%)	18 (50%)	18 (51%)	0.90	36 (51%)

Abbreviations: TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; MRI, magnetic resonance imaging; CT, computed tomography

[a] Plus-minus values are means ± 1 standard deviation.

[b] Magnetic resonance imaging interpreted by 3 independent neuroradiologists with subsequent adjudication. Scans were interpreted individually following each study visit and then again longitudinally. Longitudinal results are presented here. No participant had improved or worsened MRI findings over time.

[c] Computed tomography angiography interpreted by a neuroradiologist with CT expertise. Scans were interpreted individually following each study visit and then again longitudinally. Longitudinal results are presented here. Changes with time are presented in Table 8.

TABLE 2. Participant baseline characteristics [a]

Characteristics	HBO_2 Group (N=36)	Sham Group (N=35)	P-value	BIMA Total (N=71)
Alternative therapy usage, N (%)				
Psychotherapy	12 (33%)	7 (20%)	0.20	19 (27%)
Counseling	16 (44%)	12 (34%)	0.38	28 (39%)
Cognitive rehabilitation	3 (8%)	0 (0%)	0.24	3 (4%)
Occupational therapy	8 (22%)	7 (20%)	0.82	15 (21%)
Sleep therapy	8 (22%)	3 (9%)	0.11	11 (15%)
Physical therapy	14 (39%)	20 (57%)	0.12	34 (48%)
Potential non-trauma brain insults, N (%)	6 (17%)	4 (11%)	0.74	10 (14%)
State-Trait Anger Expression Inventory-2				
Anger Control-In	20±5	23±6	0.03	21±6
Anger Control-Out	19±5	23±6	0.02	21±6
Brain MRI, N (%) [b]				
Atrophy	13/34 (38%)	15/33 (45%)	0.62	28/67 (42%)
Cavum septum pellucidum	23/34 (68%)	27/33 (82%)	0.26	50/67 (75%)
Diffuse/traumatic axonal injury	34/35 (97%)	26/33 (79%)	0.03	60/68 (88%)
Pineal cysts or pineal changes	23/34 (68%)	18/33 (55%)	0.32	41/67 (61%)
Pituitary abnormalities	7/34 (21%)	5/33 (15%)	0.75	12/67 (18%)
Dilated perivascular spaces	28/35 (80%)	19/33 (58%)	0.06	47/68 (69%)
CT Cerebral Perfusion Abnormalities, N (%) [c]				
Blood flow	16/31 (52%)	10/27 (37%)	0.30	26/58 (45%)
Blood volume	18/31 (58%)	11/27 (41%)	0.29	29/58 (50%)
Functional delay	9/31 (29%)	6/27 (22%)	0.76	15/58 (26%)
Mean transit time	17/31 (55%)	12/27 (44%)	0.60	29/58 (50%)
Time-to-peak	16/31 (52%)	10/27 (37%)	0.30	26/58 (45%)

Abbreviations: TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; MRI, magnetic resonance imaging; CT, computed tomography

[a] Plus-minus values are means ± 1 standard deviation.

[b] Magnetic resonance imaging interpreted by 3 independent neuroradiologists with subsequent adjudication. Scans were interpreted individually following each study visit and then again longitudinally. Longitudinal results are presented here. No participant had improved or worsened MRI findings over time.

[C] Computed tomography angiography interpreted by a neuroradiologist with CT expertise. Scans were interpreted individually following each study visit and then again longitudinally. Longitudinal results are presented here. Changes with time are presented in Table 8.

cantly better than HBO_2 in any domain or subscale at 13 weeks (Figure 4). In the Automated Neuropsychological Assessment Metrics, code substitution-delayed and matching-to-sample throughputs improved in the HBO_2 group at 13 weeks in univariate testing (P=0.01, P=0.04) and longitudinal models. The HBO_2 group improved on six of seven California Verbal Learning Test-II subtests compared to sham at 13 weeks, with two subtests reaching statistical significance in univariate testing (long delayed cued recall: P=0.003, long delay recognition hits: P=0.03) and longitudinal models. At six months, differences between groups were not statistically different in most domains. The Wechsler Test of Adult Reading indicated average pre-injury intellectual functioning across groups (mean standard score 102). The Test of Memory Malingering demonstrated participants gave good effort.

TABLE 3. Baseline and change from baseline in post-concussive and post-traumatic stress disorder symptoms, total group and by PTSD diagnosis

Measure	Baseline[a]	13 weeks			6 months			12 months		
		Change score[b]	Difference in Scores Univariate Analysis[c]	Difference in Scores Longitudinal Model[d]	Change score[b]	Difference in Scores Univariate Analysis[c]	Difference in Scores Longitudinal Model[d]	Change score[b]	Difference in Scores Univariate Analysis[c]	Difference in Scores Longitudinal Model[d]
Neurobehavioral Symptom Inventory Total Score[e]										
Total study population										
Hyperbaric oxygen (n=36)	36.2 (13.9)	-3.6 (16.1)	-7.6 [-14.4, -0.7] 0.03	-3.9 [-10.0, 2.3] 0.21	-1.6 (13.1)	-1.4 [-7.9, 5.0] 0.66	-1.4 [-6.5, 3.7] 0.60	5.3 (14.9)	1.8 [-5.3, 8.9] 0.62	4.1 [-2.2, 10.5] 0.20
Sham (n=35)	31.0 (14.8)	3.9 (11.9)			-0.1 (13.2)			3.5 (13.4)		
Normal study (n=75)[f]	3.7 (3.5)	0.5 (4.8)			0.1 (2.8)					
PTSD subgroup[g]										
Hyperbaric oxygen (n=18)	42.1 (13.5)	-8.6 (18.6)	-13.3 [-24.5, -2.1] 0.02	-8.4 [-17.2, 0.4] 0.06	-2.9 (16.1)	-0.5 [-11.2, 10.1] 0.92	-5.0 [-12.5, 2.4] 0.18	3.2 (16.6)	-1.5 [-13.4, 10.4] 0.79	2.3 [-7.1, 11.7] 0.62
Sham (n=17)	37.6 (13.7)	4.8 (12.7)			-2.4 (12.5)			4.8 (14.5)		
No PTSD subgroup										
Hyperbaric oxygen (n=18)	30.3 (11.9)	1.3 (11.6)	-1.8 [-9.8, 6.1] 0.64	0.2 [-8.2, 8.7] 0.96	-0.3 (9.9)	-2.2 [-10.4, 6.0] 0.59	1.9 [-5.1, 8.8] 0.59	7.3 (13.1)	4.8 [-4.3, 13.9] 0.29	5.5 [-3.1, 14.1] 0.21
Sham (n=18)	24.7 (13.2)	3.2 (11.5)			1.9 (13.8)			2.5 (12.8)		
Posttraumatic Stress Disorder Checklist – Civilian Version Total Score[h]										
Total study population										
Hyperbaric oxygen (n=36)	46.5 (13.7)	-4.2 (16.1)	-7.3 [-13.5, -1.0] 0.02	-6.2 [-12.0, -0.4] 0.04	-1.4 (14.0)	-3.0 [-8.9, 2.9] 0.31	-3.0 [-7.8, 1.7] 0.21	8.4 (14.1)	3.3 [-3.5, 10.2] 0.34	3.8 [-2.1, 9.8] 0.20
Sham (n=35)	43.2 (14.0)	3.1 (8.4)			1.6 (9.2)			5.0 (13.4)		
Normal study (n=75)[f]	19.7 (3.5)	0.4 (4.3)			0.5 (3.8)					
PTSD subgroup[g]										
Hyperbaric oxygen (n=18)	54.9 (13.0)	-9.3 (15.6)	-12.3 [-21.4, -3.1] 0.01	-4.7 [-13.9, 4.4] 0.30	-3.7 (12.3)	-4.1 [-11.9, 3.7] 0.29	-1.1 [-9.0, 6.8] 0.78	5.8 (11.8)	0.0 [-9.1, 9.0] 0.99	6.8 [-2.5, 16.2] 0.15
Sham (n=17)	52.1 (9.1)	3.0 (9.5)			0.4 (8.6)			5.8 (13.3)		
No PTSD subgroup										
Hyperbaric oxygen (n=18)	38.0 (8.2)	0.9 (15.4)	-2.2 [-10.7, 6.2] 0.59	-6.9 [-16.1, 2.3] 0.14	0.8 (15.5)	-1.9 [-10.9, 7.1] 0.68	-4.1 [-12.0, 3.8] 0.30	10.9 (16.0)	6.6 [-4.0, 17.3] 0.21	1.9 [-7.6, 11.3] 0.69
Sham (n=18)	34.8 (12.6)	3.1 (7.5)			2.6 (9.9)			4.3 (13.9)		
Rivermead Post-Concussion Symptom Questionnaire - RPQ-3[i]										
Total study population										
Hyperbaric oxygen (n=36)	5.8 (2.9)	-0.3 (2.7)	-1.5 [-2.7, -0.3] 0.01	-1.2 [-2.3, -0.2] 0.02	-1.4 (2.7)	-1.7 [-2.9, -0.5] 0.007	-0.7 [-1.6, 0.2] 0.12	0.5 (2.9)	0.0 [-1.4, 1.4] >0.99	0.4 [-0.8, 1.5] 0.51
Sham (n=35)	4.5 (2.6)	1.2 (2.2)			0.3 (2.2)			0.5 (2.6)		
PTSD subgroup[g]										
Hyperbaric oxygen (n=18)	5.9 (3.2)	-0.2 (3.2)	-1.7 [-3.6, 0.3] 0.09	-1.7 [-3.2, -0.3] 0.02	-1.5 (2.7)	-1.7 [-3.6, 0.1] 0.07	-1.2 [-2.5, 0.1] 0.06	0.6 (2.9)	-0.1 [-1.9, 1.8] 0.93	0.0 [-1.7, 1.6] 0.97
Sham (n=17)	5.2 (2.5)	1.4 (2.3)			0.2 (2.3)			0.7 (2.2)		
No PTSD subgroup										
Hyperbaric oxygen (n=18)	5.7 (2.6)	-0.4 (2.3)	-1.4 [-3.0, 0.2] 0.08	-0.6 [-2.1, 0.9] 0.43	-1.2 (2.8)	-1.6 [-3.3, 0.1] 0.06	-0.1 [-1.4, 1.2] 0.85	0.4 (2.9)	0.1 [-2.0, 2.2] 0.94	0.9 [-0.7, 2.5] 0.27
Sham (n=18)	3.8 (2.6)	0.9 (2.2)			0.4 (2.1)			0.3 (3.1)		
Rivermead Post-Concussion Symptom Questionnaire RPQ-13[j]										
Total study population										
Hyperbaric oxygen (n=36)	29.0 (11.0)	-0.4 (12.3)	-5.0 [-10.7, 0.6] 0.08	-3.2 [-8.1, 1.7] 0.19	-3.0 (11.9)	-5.3 [-10.6, 0.1] 0.05	-1.8 [-5.7, 2.1] 0.35	5.2 (12.7)	0.2 [-5.6, 6.0] 0.95	1.2 [-3.3, 5.6] 0.60
Sham (n=35)	23.7 (11.4)	4.7 (11.1)			2.3 (9.9)			5.0 (10.4)		
PTSD subgroup[g]										
Hyperbaric oxygen (n=18)	31.8 (11.2)	-0.9 (15.3)	-5.6 [-15.2, 4.1] 0.25	-5.1 [-11.9, 1.8] 0.14	-2.5 (14.3)	-5.1 [-14.0, 3.7] 0.25	-4.6 [-9.8, 0.7] 0.09	3.9 (14.4)	-2.5 [-12.2 – 7.3] 0.61	-3.5 [-9.3, 2.3] 0.24
Sham (n=17)	28.7 (10.4)	4.7 (11.9)			2.7 (9.3)			6.3 (11.9)		
No PTSD subgroup										
Hyperbaric oxygen (n=18)	26.2 (10.3)	0.2 (8.8)	-4.5 [-11.2, 2.2] 0.18	0.6 [-6.3, 7.5] 0.86	-3.4 (9.3)	-5.4 [-12.3, 1.5] 0.12	2.8 [-2.6, 8.1] 0.30	6.4 (11.1)	2.6 [-4.6 – 9.7] 0.47	7.5 [1.7, 13.3] 0.01
Sham (n=18)	18.9 (10.4)	4.6 (10.7)			1.9 (10.7)			3.8 (9.1)		

TABLE 3 legend, next page

By STOP-Bang questionnaire, 50 participants (70%) had high risk for obstructive sleep apnea. Concomitant PTSD increased this risk (89% vs. 53% without PTSD, P=0.003) [20]. The Pittsburgh Sleep Quality Index composite score improved more at 13 weeks with HBO_2 than with sham by univariate (P=0.007) and longitudinal testing, with all eight submeasures favoring HBO_2. By sleep diary, both groups reported longer sleep times, shorter wake times after sleep onset, and improved sleep efficiency at 13 weeks (Table 6); the magnitude of improvement favored HBO_2, but changes were not significantly different between interventions. Five of seven sleep diary and actigraphy measures favored HBO_2. At six months, sleep outcomes trended back toward baseline. Restless legs and cataplexy symptoms [20] did not change.

Participants frequently reported auditory/vestibular symptoms [21], and 66 (93%) reported disability in these domains. Baseline abnormalities were observed in auditory processing, balance, oculomotor function, and reaction time [21]. At 13 weeks and six months, both intervention groups reported improvements. Participants with PTSD receiving HBO_2 had improved sensory organization test scores (P=0.04) (Table 7) and reduced complaints of veering, instability, and oscillopsia at 13 weeks, suggesting improved utilization of sensory input for functional balance. Thirty-one of 50 auditory/vestibular measures (62%) favored HBO_2, though only computerized dynamic posturography horizontal and vertical acuity reported symmetry were significantly different between groups. At six months, changes were not significant.

At baseline, BIMA participants walked shorter distances during the six-minute walk test compared to normals. Adjusting for baseline performance, participants with PTSD receiving HBO_2 walked farther at 13 weeks than those receiving sham (estimated mean difference 182 feet, P=0.04) (Table 7).

TABLE 3 legend

[a] Data expressed as mean (standard deviation).

[b] Change scores reflect the mean change from baseline to the specified assessment interval.

[c] Difference in mean change from baseline between hyperbaric oxygen and sham, 95% CI and p-value from univariate tests.

[d] Estimated difference between hyperbaric oxygen and sham in follow-up time point scores 95% CI, and p-value from post-hoc tests of longitudinal models adjusted for baseline score, study design characteristics (study site, time since most recent head injury, and chamber preference), and potential covariates (selected among age, baseline vitamin D, PTSD status).

[e] Possible range 0-88. Lower scores indicate symptom improvement.

[f] Results from Normal study.

[g] Post-traumatic stress disorder diagnosis was based on structured interview at baseline visit [16]. PTSD by intervention interaction p-values respectively, at week 13, month 6, and month 12 for Neurobehavioral Symptom Inventory Total Score: 0.09, 0.80, and 0.39; for Posttraumatic Stress Disorder Checklist – Civilian Version Total Score: 0.10, 0.71, and 0.34; for RPQ-3: 0.82, 0.94 and 0.91; for RPQ-13: 0.85, 0.96, and 0.39.

[h] Possible range 17-85. Lower scores indicate symptom improvement.

[i] Possible range of RQP-3 is 0-12; possible range of RPQ-13 is 0-52. Lower scores indicate symptom improvement.

TABLE 4 legend

[a] Data expressed as mean (standard deviation) [range]. Results at follow-up intervals represent changes from baseline. The hyperbaric oxygen group was compared to the sham group at each follow-up interval. For Neurobehavioral Symptom Inventory, Rivermead Post-Concussion Symptoms Questionnaire, PTSD Checklist, Center for Epidemiologic Studies - Depression Scale, and Beck Anxiety Inventory, lower scores indicate symptom improvement. For RAND Short-form 36, Satisfaction with Life Scale, and Stait-Trait Anger Expression Inventory, higher scores indicate improvement.

[b] P-value from univariate test of hyperbaric oxygen vs. sham change from baseline scores.

[c] P-value from post-hoc tests of differences between hyperbaric oxygen vs. sham at follow-up time points from longitudinal models adjusted for baseline score, study design characteristics (study site, time since most recent head injury, and chamber preference), and potential covariates (selected among age, baseline vitamin D, PTSD status). P-values marked N/A indicate instances where longitudinal models were not fitted because univariate testing did not indicate outcomes met criteria for further modeling (i.e. no significant within- or between-group tests at P<0.1 level on univariate testing or no significant differences between BIMA and Normal at baseline on univariate testing).

[d] From longitudinal models of outcomes adjusted for baseline values.

[e] Additional significant digits included to demonstrate significance below P>0.05 threshold.

[f] STAXI-2 not collected at 12 months.

TABLE 4. Symptoms and quality of life outcomes

Measure[a]	Possible range	Baseline			13 weeks				6 months				12 months				Overall Time-by-Intervention Interaction[d]
		HBO_2	Sham	p-value	HBO_2	Sham	p-value[b]	p-value[c]	HBO_2	Sham	p-value[b]	p-value[c]	HBO_2	Sham	p-value[b]	p-value[c]	
Neurobehavioral Symptom Inventory																	
Total Score	0-88	36.2 (13.9) [9, 67]	31.0 (14.8) [11, 62]	0.13	-3.6 (16.1) [-59, 26]	3.9 (11.9) [-16, 37]	0.03	0.21	-1.6 (13.1) [-27, 27]	-0.1 (13.2) [-30, 47]	0.66	0.60	5.3 (14.9) [-18, 37]	3.5 (13.4) [-23, 40]	0.62	0.20	0.04
Cognitive Score	0-16	8.3 (4.0) [0, 15]	7.4 (3.8) [1, 15]	0.33	-0.8 (4.1) [-12, 8]	0.9 (3.2) [-4, 8]	0.05	0.18	-0.4 (3.4) [-7, 8]	-0.3 (3.3) [-7, 7]	0.97	0.40	0.9 (3.5) [-5, 8]	0.6 (3.9) [-7, 11]	0.77	0.47	0.11
Affective Score	0-28	15.1 (5.4) [5, 25]	12.6 (5.9) [3, 27]	0.07	-2.0 (6.3) [-22, 11]	1.2 (4.6) [-7, 9]	0.02	0.06	-1.3 (5.4) [-17, 8]	-0.1 (5.4) [-15, 16]	0.38	0.20	1.6 (5.3) [-6, 12]	1.3 (5.1) [-12, 11]	0.79	0.44	0.04
Somatic Score	0-44	12.8 (6.4) [2, 30]	10.9 (6.9) [0, 24]	0.24	-0.8 (7.1) [-25, 12]	1.8 (6.7) [-11, 20]	0.13	0.43	-0.1 (6.0) [-13, 13]	0.3 (6.2) [-9, 24]	0.77	0.82	2.8 (7.5) [-10, 19]	1.7 (6.2) [-11, 20]	0.53	0.27	0.13
Rivermead Post-Concussion Symptoms Questionnaire																	
Total score	0-64	34.8 (13.1) [1, 57]	28.2 (13.5) [1, 54]	0.04	-0.7 (14.6) [-57, 31]	5.8 (12.4) [-13, 40]	0.05	0.12	-4.3 (14.0) [-33, 35]	2.6 (11.6) [-17, 35]	0.03	0.26	5.7 (14.7) [-23, 48]	5.5 (12.4) [-17, 37]	0.96	0.57	0.08
RPQ-3 score	0-12	5.8 (2.9) [0, 12]	4.5 (2.6) [0, 11]	0.05	-0.3 (2.7) [-8, 6]	1.2 (2.2) [-4, 5]	0.01	0.02	-1.4 (2.7) [-7, 3]	0.3 (2.2) [-3, 6]	0.007	0.12	0.5 (2.9) [-5, 8]	0.5 (2.6) [-3, 9]	>0.99	0.51	0.01
RPQ-13 score	0-52	29.0 (11.0) [1, 49]	23.7 (11.4) [0, 45]	0.047[e]	-0.4 (12.3) [-49, 25]	4.7 (11.1) [-10, 35]	0.08	0.19	-3.0 (11.9) [-27, 32]	2.3 (9.9) [-16, 29]	0.05	0.35	5.2 (12.7) [-21, 40]	5.0 (10.4) [-14, 32]	0.95	0.60	0.14
PTSD Checklist-Civilian Version																	
Total score	17-85	46.5 (13.7) [23, 77]	43.2 (14.0) [21, 71]	0.33	-4.2 (16.1) [-47, 49]	3.1 (8.4) [-15, 18]	0.02	0.04	-1.4 (14.0) [-28, 35]	1.6 (9.2) [-18, 29]	0.31	0.21	8.4 (14.1) [-21, 45]	5.0 (13.4) [-15, 39]	0.34	0.20	0.007
Re-experiencing score	5-25	12.5 (5.1) [5, 23]	12.0 (4.4) [5, 21]	0.66	-1.1 (6.1) [-18, 17]	0.9 (3.4) [-5, 7]	0.09	0.04	-0.5 (5.2) [-13, 16]	0.5 (3.7) [-6, 12]	0.36	0.18	2.3 (5.6) [-10, 17]	1.3 (4.4) [-6, 12]	0.46	0.50	0.009
Avoidance/ numbing score	7-35	16.7 (6.8) [7, 33]	16.3 (6.7) [7, 32]	0.81	-0.9 (6.9) [-16, 23]	1.4 (3.6) [-6, 10]	0.09	0.04	0.4 (6.3) [-14, 16]	1.3 (4.4) [-7, 14]	0.53	0.28	4.7 (6.4) [-12, 19]	3.0 (5.4) [-7, 17]	0.24	0.34	0.02
Hyperarousal score	5-35	17.3 (3.8) [11, 25]	14.9 (4.5) [6, 22]	0.02	-2.1 (4.8) [-13, 9]	0.8 (3.2) [-4, 6]	0.005	0.10	-1.3 (4.7) [-11, 8]	-0.2 (2.8) [-6, 4]	0.24	0.48	1.4 (4.3) [-7, 11]	0.7 (4.8) [-8, 10]	0.59	0.09	0.005
Center for Epidemiologic Studies - Depression Scale																	
Total score	0-60	19.9 (10.5) [2, 44]	21.2 (11.7) [6, 49]	0.63	-1.8 (8.8) [-25, 26]	1.2 (8.3) [-13, 23]	0.16	0.18	1.1 (8.5) [-16, 31]	0.3 (8.9) [-15, 33]	0.70	0.56	7.4 (10.0) [-15, 36]	5.0 (9.8) [-13, 24]	0.34	0.15	0.048[e]
Beck Anxiety Inventory																	
Total score	0-63	12.3 (7.9) [0, 33]	12.4 (8.6) [0, 35]	0.95	1.2 (10.6) [-14, 41]	1.2 (8.4) [-14, 22]	0.99	0.75	-0.7 (8.1) [-14, 30]	-0.4 (8.7) [-17, 25]	0.91	0.97	8.6 (10.0) [-8, 31]	6.5 (12.6) [-15, 39]	0.44	0.69	0.56
RAND Short-form 36 (transformed scores)																	
Physical functioning	0-100	67.2 (22.9) [10, 100]	66.4 (23.1) [25, 100]	0.88	-4.9 (16.5) [-45, 40]	0.9 (14.3) [-40, 25]	0.13	0.28	-4.6 (15.9) [-25, 50]	-1.9 (17.3) [-50, 40]	0.51	0.37	-9.6 (16.9) [-45, 25]	-5.2 (25.0) [-70, 35]	0.41	0.83	0.61
Role-physical	0-100	17.4 (32.1) [0, 100]	29.3 (40.9) [0, 100]	0.18	9.0 (31.7) [-75, 75]	1.5 (26.5) [-50, 75]	0.29	0.15	15.0 (29.8) [-25, 100]	3.9 (33.7) [-100, 100]	0.16	0.33	2.9 (39.8) [-100, 100]	9.7 (35.2) [-75, 100]	0.47	0.59	0.15
General health	0-100	51.9 (22.1) [10, 100]	48.6 (15.4) [20, 82]	0.47	1.3 (18.3) [-33, 57]	0.4 (15.0) [-30, 30]	0.83	0.94	-1.4 (12.2) [-25, 37]	-0.3 (18.0) [-25, 55]	0.78	0.57	-8.2 (13.7) [-42, 15]	-3.4 (18.3) [-37, 33]	0.24	0.22	0.38
Bodily pain	0-100	37.3 (19.3) [0, 84]	41.3 (18.4) [10, 74]	0.37	4.7 (18.0) [-21, 59]	1.7 (17.4) [-43, 40]	0.48	N/A	4.2 (17.3) [-31, 33]	2.4 (15.7) [-33, 43]	0.66	N/A	-4.4 (20.9) [-62, 51]	2.6 (18.2) [-33, 40]	0.16	N/A	N/A
Vitality	0-100	31.4 (21.6) [0, 90]	30.9 (16.5) [0, 65]	0.91	7.2 (18.5) [-20, 60]	3.9 (14.9) [-45, 40]	0.42	0.46	5.4 (13.8) [-25, 45]	5.0 (16.1) [-30, 40]	0.91	0.68	-5.0 (21.3) [-85, 30]	3.9 (23.8) [-35, 60]	0.12	0.06	0.05
Social functioning	0-100	49.3 (28.2) [0, 100]	48.2 (25.4) [0, 100]	0.86	1.7 (21.2) [-38, 50]	1.5 (22.9) [-50, 38]	0.97	N/A	1.8 (17.5) [-50, 38]	6.3 (24.8) [-50, 50]	0.39	N/A	-5.5 (31.4) [-75, 75]	5.2 (33.0) [-88, 75]	0.18	N/A	N/A
Role-emotional	0-100	49.1 (44.0) [0, 100]	45.7 (39.7) [0, 100]	0.74	0.9 (52.5) [-100, 100]	2.0 (34.3) [-100, 67]	0.92	0.68	5.7 (46.8) [-100, 100]	5.2 (35.0) [-100, 67]	0.96	0.85	-17.6 (54.6) [-100, 100]	-3.2 (51.9) [-100, 100]	0.28	0.21	0.24
Mental health	0-100	56.7 (23.0) [12, 92]	57.4 (22.4) [16, 96]	0.90	3.1 (19.3) [-48, 40]	-2.9 (15.6) [-52, 24]	0.16	0.12	4.2 (12.6) [-24, 36]	-1.0 (17.5) [-52, 40]	0.16	0.44	-9.1 (19.5) [-68, 20]	-2.3 (19.8) [-48, 36]	0.17	0.16	0.03
Satisfaction with Life Scale																	
Total score	5-35	21.8 (7.1) [6, 35]	19.1 (6.2) [9, 30]	0.09	0.9 (7.7) [-24, 13]	1.3 (5.8) [-15, 11]	0.79	0.44	1.7 (4.6) [-7, 12]	0.1 (7.0) [-20, 10]	0.28	0.88	-2.8 (6.9) [-18, 9]	0.5 (6.9) [-14, 15]	0.06	0.22	0.15
State-Trait Anger Expression Inventory 2[f]																	
Anger control-in		19.8 (5.4) [8, 32]	22.8 (5.9) [13, 32]	0.03	1.7 (5.6) [-10, 19]	-2.6 (6.8) [-21, 12]	0.005	0.001	1.0 (5.7) [-8, 19]	-1.2 (5.1) [-13, 11]	0.11	0.18					0.01
Anger control-out		19.3 (5.2) [10, 30]	22.5 (5.7) [13, 32]	0.02	1.5 (5.9) [-12, 17]	-1.1 (5.3) [-18, 5]	0.07	0.26	0.6 (5.7) [-9, 18]	-1.1 (5.4) [-15, 10]	0.20	0.56					0.50
Anger expression index		44.8 (14.3) [12, 75]	38.5 (16.1) [6, 66]	0.09	-5.3 (15.7) [-45, 39]	5.1 (17.2) [-25, 52]	0.01	0.02	-2.0 (15.2) [-43, 25]	3.0 (14.6) [-20, 45]	0.18	0.40					0.04

TABLE 4 legend, facing page

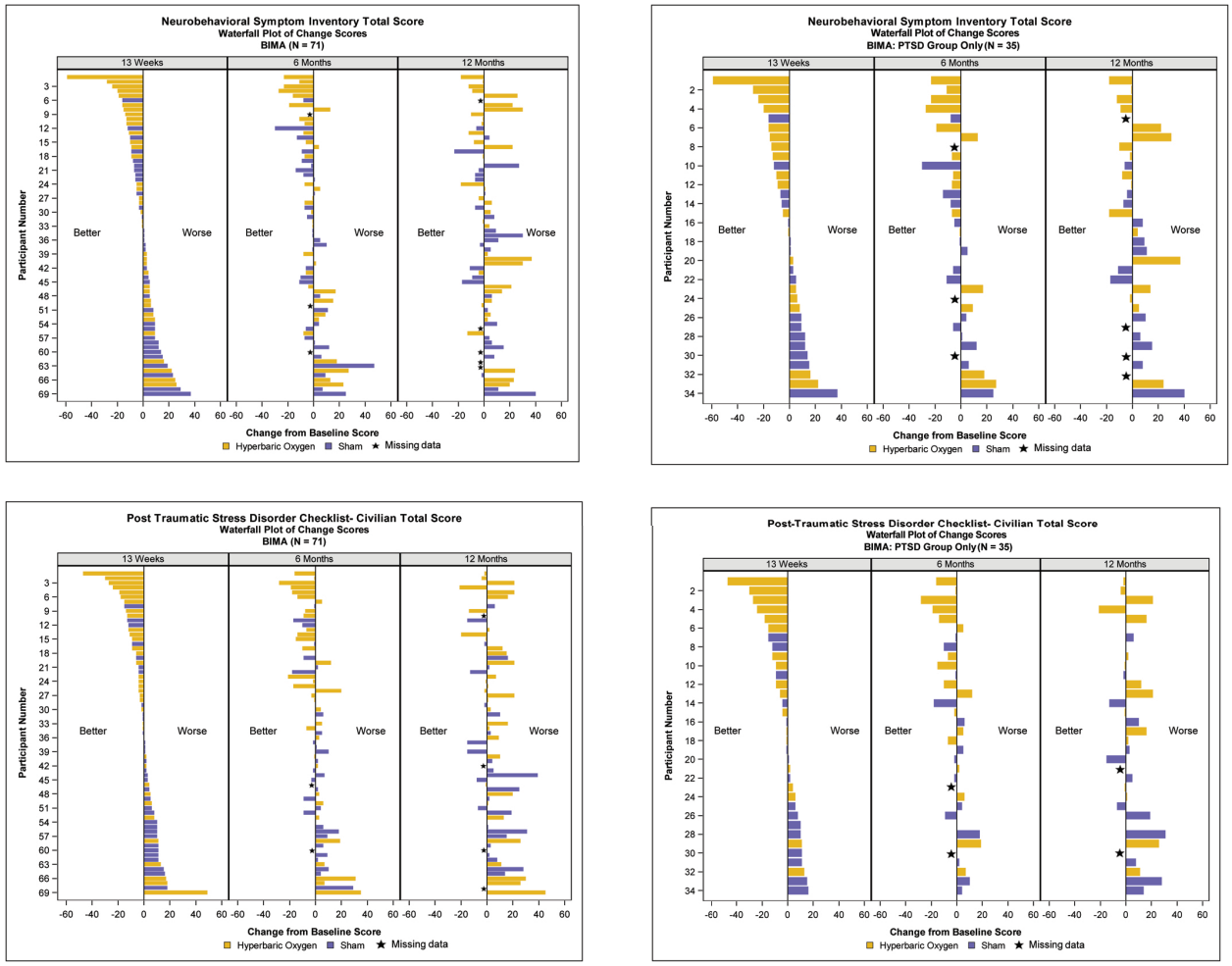

FIGURE 3. Plot of participant change scores for post-concussive and PTSD symptoms

Each bar represents Neurobehavioral Symptom Inventory (post-concussive symptoms) and Post-Traumatic Stress Disorder Checklist – Civilian Version (PTSD symptoms) scores for each participant at 13 weeks, 6 months, and 12 months, compared to baseline, for the total study group (left) and participants with PTSD (right). The change from baseline score (*x*-axis) is the numeric change in the total score of each instrument. For example, if the baseline score Neurobehavioral Symptom Inventory score was 40 and the 13-week score was 20, the change score is -20. Participants are ranked by those who improved most to least at 13 weeks. At 13 weeks, more participants receiving hyperbaric oxygen improved than sham. Most of the participants who received sham worsened or had a smaller degree of improvement. By 6 and 12 months, marked variability is evident on both measures.

Abnormal baseline neurological findings (Table 8) included near point of convergence (54%), Sharpened Romberg (49%), lower extremity sensation (20%), facial sensation (15%), tandem gait (13%), and tremor (11%) [17]. Examinations varied by intervention and time. No embellishment was detected in any participant. Baseline electroencephalogram showed generalized (37%) and localized (8%) slowing, independent of pharmacotherapy [18].

On standardized [25] clinical MRI interpretation, anatomic abnormalities were common (Table 2), without change over time. Fifty-six participants (80%) had diffuse/traumatic axonal injury manifested by T2 white matter hyperintensities (median 3 lesions, range 1-108); 14 had lesions >3 mm. More sophisticated imaging results will be presented elsewhere. Clinical interpretation of baseline cerebral blood flow by computed tomography angiography was abnormal in 26/58 participants (45%) (Table 2). At 13 weeks, cerebral blood flow improved in four HBO_2 and three sham participants. At six months, seven in each group had improved (Table 8).

Interbeat-interval (heart-rate variability) analysis from 24-hour ambulatory electrocardiogram showed baseline autonomic dysfunction (low/high frequency ratio

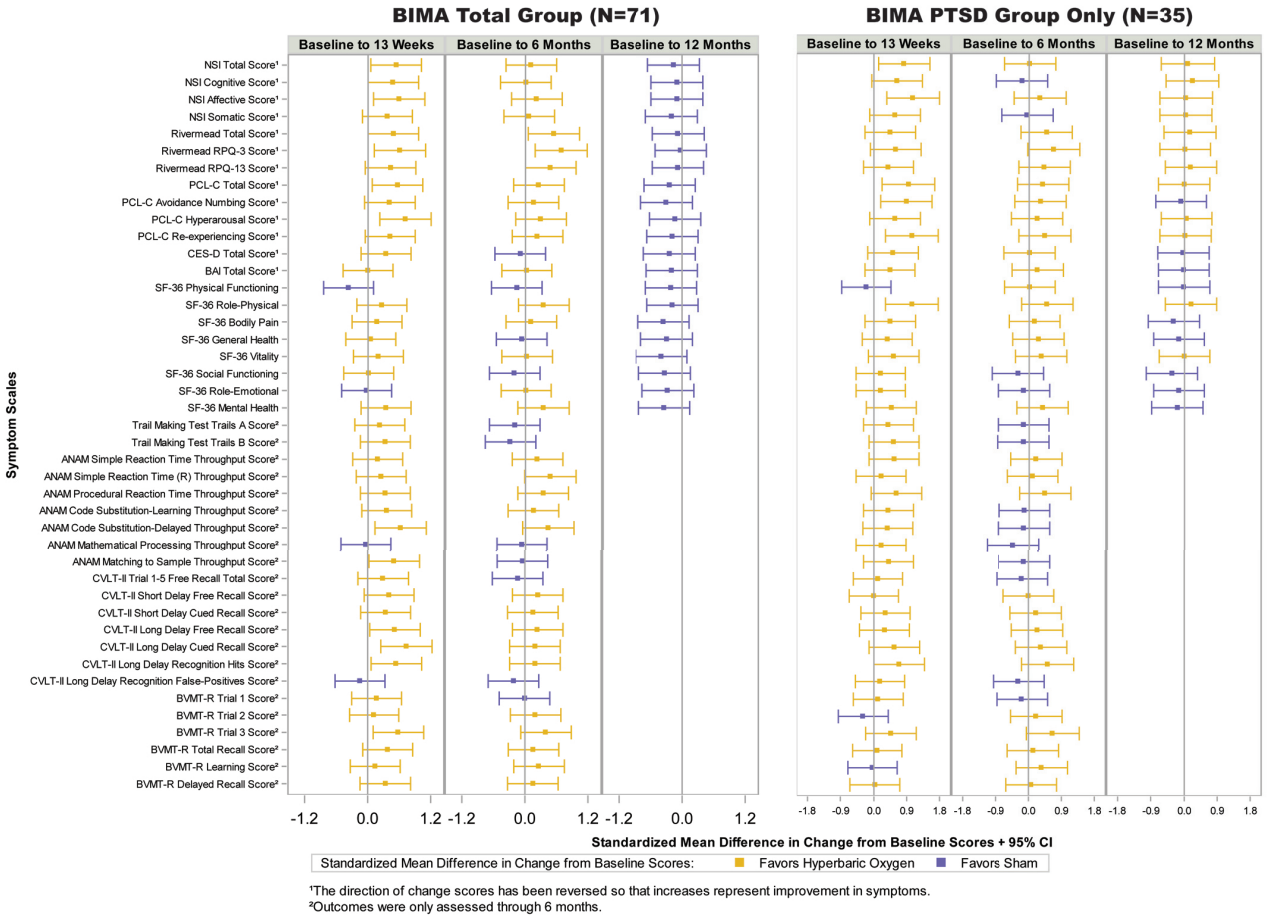

FIGURE 4. Forest plots

Neuropsychological self-reported symptoms and change from baseline for the total BIMA population and the subgroup of participants who met PTSD diagnostic criteria at baseline. The *x*-axis features a standardized mean difference and corresponding 95% CI for each outcome. The standardized mean difference is essentially an effect size measure that is calculated as the difference in change from baseline scores between the two intervention groups divided by a pooled standard deviation.

Abbreviations: NSI, Neurobehavioral Symptom Inventory; PCL-C, Post-Traumatic Stress Disorder Checklist – Civilian version; CES-D, Centers for Epidemiological Studies – Depression scale; BVMT-R, Brief Visuospatial Memory Test – Revised; BAI, Beck Anxiety Inventory; SF-36, RAND Short-Form 36; ANAM, Automated Neuropsychological Assessment Metrics; CVLT-II, California Verbal Learning Test – Second Edition

>1.0) in 77% [19]. HBO_2 participants with PTSD improved for very low, low, and high frequency power (longitudinal model overall time by intervention by PTSD interaction terms P=0.001, P=0.0003, P=0.006 respectively) (Table 9). From longitudinal models, maximal effects were seen at six months, where low and very low frequency power decreased and high frequency power increased, indicating a spectral power shift toward normal for this subgroup (Table 9).

CD34+ stem cells were normal at all time points.

Seventy-one BIMA participants underwent 2,722 chamber sessions with no serious adverse events related to participation. Some minor non-limiting barotrauma occurred during 43 chamber sessions in 25 participants: middle ear (HBO_2 n=12, sham n=5) and sinus (HBO_2 n=5, sham n=3). No participant experienced in-chamber claustrophobia. One discontinued HBO_2 at 33 sessions for vision complaints (Figure 2). Participants were informed they had an equal chance to receive HBO_2 or sham and, when questioned, remained unaware of allocation (P>0.99).

Post-concussive and PTSD symptoms were analyzed for age (≤32 vs. >32 years), interval since injury, number

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TABLE 5. Results of neuropsychological testing

Measure[a]	Domain	Baseline			13 weeks				6 months				Overall Time by Intervention Interaction[d]
		HBO_2	Sham	p-value	HBO_2	Sham	p-value[b]	p-value[c]	HBO_2	Sham	p-value[b]	p-value[c]	
Weschler Test of Adult Reading, standard score													
Standard score	Pre-injury intellectual functioning	102 (10) [63, 120]	103 (11) [76, 122]	0.79	0.2 (4.2) [-11, 9]	0.1 (4.0) [-8, 9]	0.96	0.78	2.3 (4.2) [-6, 10]	1.2 (4.6) [-10, 10]	0.31	0.24	0.32
Test of Memory Malingering, no. (%)													
Retention trial score <45	Effort	2 (6)	3 (9)	0.67	2 (6)	1 (3)	0.60	N/A	1 (3)	0 (0)	0.34	N/A	N/A
Automated Neuropsychological Assessment Metrics, throughput standard score													
Simple reaction time	Processing speed, attention	77 (26) [23, 112]	84 (31) [0, 122]	0.31	9.1 (26.5) [-42, 74]	4.7 (20.0) [-37, 59]	0.44	0.82	5.5 (31.6) [-78, 63]	-0.7 (22.3) [-87, 32]	0.36	0.62	0.47
Simple reaction time-repeat	Effect of fatigue on processing speed	65 (29) [6, 117]	71 (32) [-4, 123]	0.39	12.6 (29.5) [-42, 86]	5.0 (30.5) [-36, 81]	0.30	0.47	13.7 (30.5) [-79, 87]	-1.2 (32.4) [-115, 53]	0.06	0.01	0.14
Procedural reaction time	Processing speed, attention	80 (27) [10, 122]	87 (24) [21, 124]	0.26	18.7 (32.1) [-98, 94]	8.6 (29) [-45, 100]	0.18	0.39	8.9 (28.8) [-66, 86]	-0.6 (27.1) [-79, 52]	0.17	0.55	0.80
Code substitution-learning	Visual scanning, perception, attention, associative learning, information processing	95 (22) [50, 136]	97 (19) [62, 134]	0.70	1.1 (16.1) [-25, 54]	-4.2 (13.6) [-29, 29]	0.15	0.20	4.9 (17.6) [-32, 47]	2.5 (14.8) [-38, 28]	0.54	0.69	0.53
Code substitution-delayed	Learning and delayed memory	92 (16) [68, 133]	99 (19) [68, 133]	0.12	10.0 (12.2) [-15, 30]	2.2 (13) [-18, 30]	0.01	0.03	10.5 (13.9) [-27, 46]	4.9 (11.7) [-21, 26]	0.08	0.21	0.34
Mathematical processing	Computational skills, concentration, working memory	93 (15) [63, 125]	94 (20) [58, 175]	0.73	-0.4 (11.5) [-21, 34]	0.1 (11.5) [-21, 24]	0.88	0.34	2.7 (12.1) [-24, 28]	3.4 (10.2) [-22, 18]	0.79	0.55	0.78
Matching to sample	Processing speed, working memory	89 (20) [58, 142]	93 (18) [61, 145]	0.42	8.4 (14.2) [-23, 44]	1.6 (12.8) [-30, 28]	0.04	0.03	3.9 (15.4) [-32, 35]	4.5 (12.9) [-23, 28]	0.86	0.61	0.02
California Verbal Learning Test-II, standard score													
Trial 1-5 free recall	Verbal learning, memory	45.9 (11.8) [22, 69]	45.5 (12.2) [18, 62]	0.90	1.6 (6.5) [-13, 13]	-0.8 (9.6) [-36, 15]	0.22	0.12	4.1 (7.6) [-14, 22]	5.3 (8.4) [-18, 22]	0.57	0.64	0.07
Short delay free recall		-0.6 (1.3) [-3, 2]	-0.5 (1.4) [-3, 2]	0.86	0.2 (0.8) [-1.5, 2]	-0.2 (1.1) [-3.5, 3.5]	0.10	0.11	0.6 (1.2) [-3, 3]	0.3 (1.0) [-2, 3]	0.32	0.23	0.68
Short delay cued recall		-0.5 (1.2) [-3, 1.5]	-0.5 (1.3) [-3, 1.5]	>0.99	0.2 (0.9) [-1.5, 2.5]	-0.1 (0.9) [-2.5, 2.5]	0.16	0.16	0.4 (0.9) [-1.5, 2]	0.3 (1.0) [-2.5, 3]	0.52	0.31	0.75
Long delay free recall		-0.9 (1.4) [-3, 1.5]	-0.7 (1.4) [-3.5, 1.5]	0.62	0.5 (1.1) [-1.5, 3.5]	-0.1 (1.1) [-3, 3.5]	0.04	0.17	0.6 (1.2) [-1.5, 3]	0.4 (1.0) [-2, 3.5]	0.33	0.65	0.38
Long delay cued recalled		-0.8 (1.2) [-3.5, 1.5]	-0.6 (1.3) [-3.5, 1.5]	0.53	0.5 (0.8) [-1, 2.5]	-0.2 (1.1) [-3.5, 3]	0.003	0.003	0.5 (0.9) [-1, 3]	0.4 (0.8) [-1.5, 3]	0.44	0.36	0.04
Long delay recognition hits		-1.6 (1.9) [-5, 1]	-1.2 (1.7) [-5, 0.5]	0.38	0.4 (1.3) [-1.5, 3.5]	-0.3 (1.5) [-5, 2]	0.03	0.03	0.5 (1.6) [-3, 4.5]	0.2 (1.4) [-2, 4]	0.43	0.47	0.22
Long delay recognition false positives		0.0 (1.0) [-1, 2.5]	-0.1 (1.1) [-1, 3.5]	0.91	0.0 (1.1) [-3.5, 2.5]	0.1 (1.1) [-3, 3]	0.54	0.33	-0.3 (1.1) [-3.5, 3]	-0.1 (1.0) [-3, 2]	0.39	0.18	0.76
Brief Visuospatial Memory Test-Revised, standard score													
Trial 1	Visuospatial memory	35.8 (11.5) [20, 64]	40.4 (12.3) [20, 70]	0.11	5.8 (13.5) [-24, 42]	3.5 (13.9) [-19, 30]	0.48	0.99	2.6 (12.5) [-20, 35]	2.7 (12.3) [-30, 20]	0.99	0.41	0.43
Trial 2		39.4 (12.7) [20, 62]	41.7 (12.4) [20, 65]	0.44	1.7 (12.3) [-22, 23]	0.2 (10.9) [-22, 23]	0.61	N/A	3.3 (13.3) [-19, 34]	0.8 (10.8) [-22, 17]	0.41	N/A	N/A
Trial 3		38.0 (12.8) [20, 63]	41.1 (11.4) [20, 62]	0.30	2.0 (11.9) [-23, 31]	-5.1 (12.2) [-28, 19]	0.02	0.09	1.1 (13.2) [-29, 25]	-3.4 (9.3) [-33, 15]	0.11	0.59	0.30
Total recall		35.8 (11.5) [20, 64]	39.6 (12.3) [20, 64]	0.18	4.4 (10.6) [-17, 28]	0.2 (11.1) [-20, 20]	0.12	0.17	2.5 (11.8) [-24, 23]	0.8 (9.9) [-31, 17]	0.52	0.95	0.25
Learning		56.8 (13.9) [29, 80]	54.7 (12.1) [28, 80]	0.50	-4.9 (18.8) [-45, 29]	-7.4 (15.1) [-40, 24]	0.54	0.09	-2.1 (16.3) [-40, 29]	-5.9 (11.1) [-23, 29]	0.28	0.07	0.90
Delayed recall		39.8 (13.4) [20, 64]	40.2 (11.5) [20, 63]	0.91	3.5 (10.5) [-12, 28]	-0.3 (12.2) [-28, 23]	0.17	0.06	1.2 (12.6) [-19, 28]	-1.1 (17.0) [-53, 33]	0.52	0.22	0.58

[a] Data presented as mean (standard deviation [range] unless otherwise noted.

[b] P-value from univariate test of hyperbaric oxygen vs. sham change from baseline scores.

[c] P-value from post-hoc tests of differences between hyperbaric oxygen vs. sham at follow-up time points from longitudinal models adjusted for baseline score, study design characteristics (study site, time since most recent head injury, and chamber preference), and potential covariates (selected among age, baseline vitamin D, PTSD status). P-values marked N/A indicate instances where longitudinal models were not fitted because univariate testing did not indicate outcomes met criteria for further modeling (i.e., no significant within- or between-group tests at P<0.1 level on univariate testing or no significant differences between BIMA and Normal at baseline on univariate testing).

[d] From longitudinal models of outcomes adjusted for baseline values.

TABLE 6. Sleep outcomes

Measure	Baseline	13 weeks			6 months		
		Change score[a]	Univariate Difference in Scores [95% CI] p-value[b]	Longitudinal Model Difference in Scores [95% CI] p-value[c]	Change score[a]	Univariate Difference in Scores [95% CI] p-value[b]	Longitudinal Model Difference in Scores [95% CI] p-value[c]
Pittsburgh Sleep Quality Index[d]							
Total study population							
Hyperbaric oxygen (n=36)	14.1 (3.8)	-2.8 (4.1)	-2.5 [-4.3, -0.7] 0.007	-2.0 [-3.5, -0.4] 0.02	-1.7 (3.5)	-1.5 [-3.2, 0.2] 0.09	-1.2 [-2.8, 0.4] 0.14
Sham (n=35)	12.8 (3.7)	-0.3 (3.1)			-0.2 (3.6)		
Normal study (n=75)[e]	3.8 (2.2)						
PTSD subgroup[f]							
Hyperbaric oxygen (n=18)	14.6 (3.6)	-3.7 (4.9)	-2.3 [-5.1, 0.5] 0.11	-2.2 [-4.4, -0.0] 0.05	-2.1 (4.3)	-2.1 [-4.8, 0.5] 0.11	-1.5 [-3.7, 0.8] 0.19
Sham (n=17)	14.2 (2.6)	-1.4 (2.7)			0.0 (2.6)		
No PTSD subgroup							
Hyperbaric oxygen (n=18)	13.6 (4.1)	-1.8 (3.0)	-2.6 [-4.7, -0.5] 0.02	-1.9 [-4.1, 0.4] 0.11	-1.2 (2.6)	-0.9 [-3.4, 1.5] 0.45	-0.9 [-3.1, 1.4] 0.43
Sham (n=18)	11.4 (4.1)	0.8 (3.1)			-0.3 (4.4)		
Sleep Diary							
Total sleep time, minutes							
Hyperbaric oxygen (n=36)	301 (113)	46 (110)	37 [-18, 92] 0.18	N/A	-0.4 (134)	-0.7 [-69, 68] 0.98	N/A
Sham (n=35)	302 (119)	9 (119)			0.3 (148)		
Normal study (n=75)[e]	431 (45)						
Wake time after sleep onset, minutes							
Hyperbaric oxygen (n=36)	46 (53)	-26 (50)	-1 [-26, 24] 0.92	N/A	-4 (60)	7 [-22, 36] 0.62	N/A
Sham (n=35)	59 (57)	-25 (55)			-11 (57)		
Sleep maintenance efficiency, %							
Hyperbaric oxygen (n=29)	84.8 (15.6)	7.5 (14.9)	0.5 [-9.0, 10.0] 0.91	N/A	0.5 (21.8)	-4.2 [-16.0, 7.5] 0.47	N/A
Sham (n=31)	80.8 (17.6)	6.9 (20.1)			4.7 (19.9)		
Actigraphy							
Total sleep time, minutes							
Hyperbaric oxygen (n=35)	414 (63)	-4 (141)	-45 [-121, 31] 0.24	N/A	5 (88)	-67 [-139, 5] 0.07	N/A
Sham (n=35)	387 (63)	41 (150)			72 (181)		
Normal study (n=75)[e]	409 (53)						
Wake time after sleep onset, minutes							
Hyperbaric oxygen (n=35)	42 (16)	-4 (15)	-8 [-16, 0] 0.06	N/A	-1 (14)	5 [-4, 14] 0.31	N/A
Sham (n=35)	44 (20)	4 (16)			-5 (21)		
Sleep maintenance efficiency, %							
Hyperbaric oxygen (n=35)	91.0 (3.1)	0.6 (3.3)	0.7 [-1.0, 2.4] 0.42	N/A	0.1 (2.6)	-1.9 [-4.0, 0.1] 0.06	N/A
Sham (n=35)	89.9 (5.0)	-0.1 (3.3)			2.1 (5.1)		

[a] Mean change from baseline to specified assessment interval. Data expressed as mean (standard deviation).

[b] Difference in mean change from baseline between hyperbaric oxygen and sham, 95% confidence interval and P-value from univariate tests.

[c] Estimated difference between hyperbaric oxygen and sham in follow-up time point scores, 95% confidence interval, and P-value from post-hoc tests of longitudinal models adjusted for baseline score, study design characteristics (study site, time since most recent head injury, and chamber preference), and potential covariates (selected among age, baseline vitamin D, PTSD status). P-values marked N/A indicate instances where longitudinal models were not fitted because univariate testing did not indicate outcomes met criteria for further modeling (i.e., no significant within- or between-group tests at P<0.1 level on univariate testing or no significant differences between BIMA and Normal at baseline on univariate testing).

[d] Possible range 0-35 [65]. Higher scores indicate poor sleep quality.

[e] Results from Normal study.

[f] Post-traumatic stress disorder diagnosis was based on structured interview at baseline visit.[16] PTSD by intervention interaction P-values, respectively, at week 13 and month 6 for Pittsburgh Sleep Quality Index: 0..86 and 0.50.

TABLE 7. Sensory organization test and six-minute walk test outcomes

Measure	Baseline	13 weeks		6 months	
		Change score[a]	p-value [95% CI][b]	Change score[a]	p-value [95% CI][b]
Sensory organization test composite score[c]					
Total study population					
Hyperbaric oxygen (n=34)	71.2 (13.9)	6.4 (13.9)	0.65 [-5.0, 7.9]	6.8 (14.7)	0.51 [-4.7, 9.5]
Sham (n=35)	68.1 (17.1)	4.9 (12.2)		4.5 (13.3)	
Normal study (n=75)[d]	79.5 (5.9)	2.9 (4.7)		3.0 (5.1)	
PTSD subgroup[e]					
Hyperbaric oxygen (n=17)	68.1 (16.6)	10.3 (15.9)	0.04[f] [0.5, 19.7]	9.8 (17.4)	0.22 [-4.6, 19.4]
Sham (n=17)	65.5 (17.7)	0.2 (9.5)		2.4 (14.1)	
No PTSD subgroup					
Hyperbaric oxygen (n=17)	74.2 (10.2)	2.5 (10.7)	0.12 § [-14.9, 1.8]	4.1 (11.5)	0.61 [-10.8, 6.4]
Sham (n=18)	70.5 (16.6)	9.1 (13.1)		6.3 (12.7)	
6-minute walk test distance walked, feet					
Total study population					
Hyperbaric oxygen (n=36)	1652 (303)	62 (253)	0.12 [-25, 223]	-68 (329)	0.87 [-162, 137]
Sham (n=35)	1785 (374)	-37 (254)		-55 (253)	
Normal study (n=75)[d]	1840 (267)				
PTSD subgroup[e]					
Hyperbaric oxygen (n=18)	1596 (254)	55 (300)	0.07[g] [-13, 400]	-113 (342)	0.73 [-181, 257]
Sham (n=17)	1731 (399)	-139 (261)		-151 (230)	
No PTSD subgroup					
Hyperbaric oxygen (n=18)	1709 (343)	69 (205)	0.76 [-124, 169]	-25 (320)	0.56 [-265, 147]
Sham (n=18)	1835 (352)	47 (222)		34 (247)	

[a] Mean change from baseline to specified assessment interval. Data expressed as mean (standard deviation).

[b] Statistical significance of between-group (hyperbaric oxygen and sham) comparison and 95% confidence interval of change in mean difference.

[c] Evaluates the role of sensory inputs (vision, vestibular, somatosensory) in functional balance [79].

[d] Results from Normal study.

[e] Post-traumatic stress disorder diagnosis was based on structured interview at baseline visit [16].

[f] PTSD by intervention interaction P-values, respectively, at week 13 and month 6 for Sensory organization test composite score: 0.01 and 0.18; for 6-minute walk test distance walked: 0.17 and 0.51.

[g] After adjusting for baseline total distance walked, post-hoc tests indicated a significant improvement (increase) in the hyperbaric oxygen PTSD subgroup at 13 weeks in total distance walked compared to sham PTSD subgroup (estimated mean difference at 13 weeks = 182.02, 95% CI: [11.50, 352.54], P: 0.04).

TABLE 8. Neurological and computed tomography angiography brain perfusion findings

	Baseline Abnormality N (%[a])	Baseline to 13 Weeks			Baseline to 6 Months		
		No change	Normal to abnormal	Abnormal to normal	No change	Normal to abnormal	Abnormal to normal
Neurological evaluation							
Near point of convergence >12.7 cm							
Hyperbaric oxygen (n=36)	22 (61)	25 (69)	5 (14)	6 (17)	25 (71)	4 (11)	6 (17)
Sham (n=35)	16 (46)	22 (67)	7 (21)	4 (12)	23 (72)	7 (22)	2 (6)
Sharpened Romberg							
Hyperbaric oxygen (n=36)	13 (36)	28 (82)	2 (6)	4 (12)	23 (66)	6 (17)	6 (17)
Sham (n=34)	21 (62)	19 (66)	1 (3)	9 (31)	17 (57)	3 (10)	10 (33)
Lower extremity sensory testing (thermal)							
Hyperbaric oxygen (n=36)	6 (17)	29 (81)	1 (3)	6 (17)	28 (80)	1 (3)	6 (17)
Sham (n=35)	8 (23)	29 (88)	1 (3)	3 (9)	27 (84)	1 (3)	4 (13)
Facial sensation							
Hyperbaric oxygen (n=36)	3 (8)	31 (86)	2 (6)	3 (8)	29 (83)	3 (9)	3 (9)
Sham (n=35)	8 (23)	30 (91)	0 (0)	3 (9)	29 (91)	0 (0)	3 (9)
Tandem gait							
Hyperbaric oxygen (n=36)	3 (8)	34 (97)	0 (0)	1 (3)	31 (91)	1 (3)	2 (6)
Sham (n=33)	6 (18)	25 (83)	1 (3)	4 (13)	25 (86)	1 (3)	3 (10)
Tremor							
Hyperbaric oxygen (n=36)	7 (19)	31 (86)	1 (3)	4 (11)	27 (77)	2 (6)	6 (17)
Sham (n=35)	1 (3)	32 (97)	1 (3)	0 (0)	31 (97)	1 (3)	0 (0)
Electroencephalography							
Generalized slowing							
Hyperbaric oxygen (n=36)	12 (33)	29 (81)	4 (11)	3 (8)	26 (74)	4 (11)	5 (14)
Sham (n=35)	14 (40)	27 (82)	3 (9)	3 (9)	22 (69)	6 (19)	4 (13)
Localized slowing							
Hyperbaric oxygen (n=36)	2 (6)	35 (97)	0 (0)	1 (3)	33 (94)	0 (0)	2 (6)
Sham (n=35)	4 (11)	28 (85)	2 (6)	3 (9)	29 (91)	0 (0)	3 (9)

	Baseline Abnormality N (%)	Baseline to 13 Weeks			Baseline to 6 Months		
		No change[b]	Worse	Better	No change†	Worse	Better
Computed tomography angiography							
Cerebral blood flow							
Hyperbaric oxygen (n=31)	16 (52)	27 (87)	0 (0)	4 (13)	24 (77)	0 (0)	7 (23)
Sham (n=27)	10 (37)	24 (89)	0 (0)	3 (11)	20 (74)	0 (0)	7 (26)
Cerebral blood volume							
Hyperbaric oxygen (n=31)	18 (58)	27 (87)	0 (0)	4 (13)	24 (77)	0 (0)	7 (23)
Sham (n=27)	11 (41)	23 (85)	0 (0)	4 (15)	20 (74)	0 (0)	7 (26)
Functional delay							
Hyperbaric oxygen (n=31)	9 (29)	30 (97)	0 (0)	1 (3)	28 (90)	0 (0)	3 (10)
Sham (n=27)	6 (22)	25 (93)	1 (4)	1 (4)	25 (93)	0 (0)	2 (7)
Mean transit time							
Hyperbaric oxygen (n=31)	17 (55)	26 (84)	0 (0)	5 (16)	24 (77)	0 (0)	7 (23)
Sham (n=27)	12 (44)	23 (85)	0 (0)	4 (15)	22 (81)	0 (0)	5 (19)
Time-to-peak							
Hyperbaric oxygen (n=31)	16 (52)	25 (81)	0 (0)	6 (19)	23 (74)	0 (0)	8 (26)
Sham (n=27)	10 (37)	22 (81)	1 (4)	4 (15)	20 (74)	0 (0)	7 (26)

[a] Percentages based on non-missing observations at each time point.

[b] Number includes participants who had no finding identified at baseline and those whose longitudinal read was the same post-baseline.

TABLE 9. Holter heart rate variability outcomes (sleep segment of 24-hour electrocardiogram)

Measure	Baseline	13 weeks			6 months		
		Change score[a]	Univariate Difference in Scores [95% CI] p-value[b]	Longitudinal Model Difference in Scores/Ratio of Scores [95% CI] p-value[c]	Change score[a]	Univariate Difference in Scores [95% CI] p-value[b]	Longitudinal Model Difference in Scores/Ratio of Scores [95% CI] p-value[c]
Very Low Frequency (Normalized Units)							
Total study population							
Hyperbaric oxygen (n=31)	222.4 (137.7)	-24.2 (151.4)	-11.6 [-82.5, 59.2] 0.74	1.3 [0.9, 1.8] 0.21	-70.5 (136.3)	-62.6 [-131.7, 6.5] 0.07	1.0 [0.7, 1.4] 0.89
Sham (n=30)	149.3 (82.8)	-12.5 (81.1)			-7.9 (100.1)		
Normal study (n=64)[d]	142.8 (86.5)	6.2 (100.2)			8.0 (121.1)		
PTSD subgroup[e]							
Hyperbaric oxygen (n=18)	247.7 (151.9)	-23.4 (133.8)	18.6 [-83.5, 120.7] 0.71	1.7 [1.0, 2.7] 0.05	-103.1 (111.0)	-108.9 [-197.3,-20.5] 0.02	0.7 [0.4, 1.2] 0.18
Sham (n=13)	168.0 (82.3)	-42.0 (97.5)			5.8 (97.8)		
No PTSD subgroup							
Hyperbaric oxygen (n=13)	187.3 (111.5)	-25.1 (177.1)	-35.2 [-142.9, 72.4] 0.51	1.0 [0.6, 1.6] 0.89	-23.1 (160.2)	-4.6 [-117.4, 108.1] 0.93	1.6 [1.0, 2.7] 0.08
Sham (n=17)	135.0 (82.8)	10.1 (60.4)			-18.4 (104.4)		
Low Frequency (Normalized Units)							
Total study population							
Hyperbaric oxygen (n=31)	109.9 (50.8)	-16.4 (49.5)	-14.4 [-39.6, 10.7] 0.25	1.1 [0.9, 1.5] 0.43	-27.0 (51.2)	-26.0 [-54.3, 2.2] 0.07	1.0 [0.7, 1.3] 0.81
Sham (n=30)	81.5 (44.9)	-1.9 (36.5)			-1.0 (47.5)		
Normal study (n=64)[d]	75.1 (38.8)	5.4 (41.1)			2.3 (48.3)		
PTSD subgroup[e]							
Hyperbaric oxygen (n=18)	119.8 (59.2)	-22.2 (55.7)	-2.1 [-43.5, 39.3] 0.92	1.3 [0.9, 1.8] 0.22	-42.1 (47.3)	-49.0 [-91.2, -6.8] 0.02	0.7 [0.5, 1.0] 0.03
Sham (n=13)	87.6 (43.7)	-20.1 (36.4)			6.9 (55.9)		
No PTSD subgroup							
Hyperbaric oxygen (n=13)	96.2 (33.9)	-9.1 (41.9)	-21.1 [-51.5, 9.2] 0.16	1.0 [0.7, 1.4] 0.86	-5.1 (50.6)	2.0 [-36.8, 40.8] 0.92	1.4 [1.0, 2.1] 0.07
Sham (n=17)	76.9 (46.6)	12.0 (31.0)			-7.0 (41.2)		
High Frequency (Normalized Units)							
Total study population							
Hyperbaric oxygen (n=31)	47.8 (12.1)	3.5 (9.1)	3.4 [-1.9, 8.6] 0.20	-0.1 [-5.5, 5.4] 0.98	-1.9 (14.2)	3.9 [-4.1, 12.0] 0.33	-0.3 [-8.0, 7.4] 0.95
Sham (n=30)	55.1 (12.1)	0.1 (9.1)			-5.9 (13.9)		
Normal study (n=64)[d]	56.4 (12.3)	-1.2 (9.0)			-1.3 (8.7)		
PTSD subgroup[e]							
Hyperbaric oxygen (n=18)	45.7 (12.3)	3.5 (9.3)	1.6 [-7.1, 10.3] 0.70	-2.9 [-10.5, 4.6] 0.44	1.8 (13.3)	10.8 [-1.1, 22.7] 0.07	6.3 [-4.3, 16.8] 0.24
Sham (n=13)	55.3 (12.5)	1.9 (11.8)			-9.0 (15.7)		
No PTSD subgroup							
Hyperbaric oxygen (n=13)	50.6 (11.7)	3.4 (9.3)	4.6 [-2.0, 11.3] 0.16	3.2 [-4.5, 10.9] 0.40	-7.3 (14.2)	-3.9 [-15.1, 7.4] 0.49	-7.4 [-18.4, 3.6] 0.18
Sham (n=17)	54.9 (12.2)	-1.3 (6.6)			-3.5 (12.5)		

[a] Mean change from baseline to specified assessment interval. Data expressed as mean (standard deviation).

[b] Difference in mean change from baseline between hyperbaric oxygen and sham, 95% confidence interval and p-value from univariate tests.

[c] Estimates provided from post-hoc tests of longitudinal models of follow-up time point scores adjusted for baseline score, study design characteristics (study site, time since most recent head injury, and chamber preference), and potential covariates (selected among age, baseline vitamin D, PTSD status). For very low and low frequency normalized units models, a natural log transformation was applied to outcomes to satisfy model assumptions. Hypothesis testing was performed on the log scale and post-hoc mean estimates were back-transformed so as to be interpreted on the original scale of the response; the back-transformed estimate of two least square means on the log scale is interpreted as a ratio of the geometric means for hyperbaric oxygen and sham, 95% confidence interval for the ratio, and p-value. For high frequency power, the estimated difference between hyperbaric oxygen and sham scores, 95% confidence interval, and P-value are provided.

[d] Results from Normal study.

[e] Post-traumatic stress disorder diagnosis was based on structured interview at baseline visit.[16] PTSD by intervention interaction p-values, respectively, at week 13 and month 6 for Very Low Frequency (Normalized Units): 0.46 and 0.14; for Low Frequency (Normalized Units): 0.45 and 0.07; for High Frequency (Normalized Units): 0.57 and 0.07.

of injuries, and trauma type (blunt force only vs. ≥1 blast) (Table 10). At 13 weeks, younger participants receiving HBO_2 had improved NSI total, affective, and somatic scores (P=0.008, P=0.01, and P=0.009) and PTSD Checklist total and hyperarousal scores (P=0.03 and P=0.005).

Neither interval since injury nor number of injuries influenced 13-week scores, but in participants with ≥1 blast injury, the NSI and PTSD Checklist total scores improved in the HBO_2 group (P=0.02 and P=0.03). Because almost all participants with PTSD had blast injury, the effect of HBO_2 on blast injury in participants with PTSD cannot be determined, but these results suggest correlation between blast and PTSD.

The modified Generalized Least Squares (GLS) global point estimates favored HBO_2: BIMA total 0.45 (95% CI-0.03-0.93), PTSD subgroup 0.73 (0.04-1.43), no-PTSD subgroup 0.07 (-0.06-0.74) (Figure 5).

DISCUSSION

In BIMA, participants receiving HBO_2 had improved post-concussive and PTSD symptoms, sleep quality, and some anger and memory outcomes compared to sham at 13 weeks. Improvements with HBO_2 were sometimes larger in participants with PTSD. The magnitude of improvement was clinically meaningful but did not restore BIMA participants to normal. Most point estimates for symptoms, quality of life, sleep, neuropsychological, and auditory/vestibular domains favored HBO_2 at 13 weeks. By six months, improvements variably diminished. Including these measures in future studies may be useful.

Despite its comprehensive assessments, BIMA did not answer how HBO_2 improved symptoms. Though BIMA employed a rigid definition of mild TBI and excluded other brain injuries, neuroimaging ranged from normal to moderate TBI, suggesting discordance between neuro-imaging and clinical presentation. BIMA participants had many other abnormal findings [17-22]. However, except possibly heart rate variability, exploratory measures linked to mechanisms of action (e.g., cerebral perfusion, electroencephalography, CD34+ mobilization) did not change over time or consistently favor one intervention over another. BIMA did not investigate potential mechanisms such as non-CD34+ stem cells [26], neurotransmitters, neuronal/axonal function, cerebrospinal fluid or subclinical inflammation.

From prior HBO_2 studies for post-concussive symptoms, some suggested improvements result from "intense ritual experience" [11,27] driving placebo/Hawthorne effects [28]. Some speculate hyperbaric shams improve brain damage [7,29,34]; others disagree [28]. BIMA does not support placebo effects or sham exposures improving patient-reported outcomes. Other potential explanations for BIMA results include multiplicity, regression to the mean, testing methodology, or true HBO_2 effect.

These analyses were not adjusted for multiplicity. In exploratory, hypothesis-generating studies, we tolerate the increase in Type I error inherent in multiple testing because recommendations for further investigation are not based on a single P-value (as in efficacy trials), but on the data in totality. Given the large number of outcome measures, it would be anticipated that some of the measures tested would reach statistical significance at the P<0.05 level by chance. However, statistically significant improvements and point estimates for the majority of outcomes favored HBO_2, which would not be expected. Interpreting BIMA must rely on consistent findings within-study and across other studies. In BIMA, change scores on measures used in prior U.S. military studies favored HBO_2. The results in the HBO_2 arm do not conflict with the prior studies, and they suggest that a Phase III efficacy study is warranted.

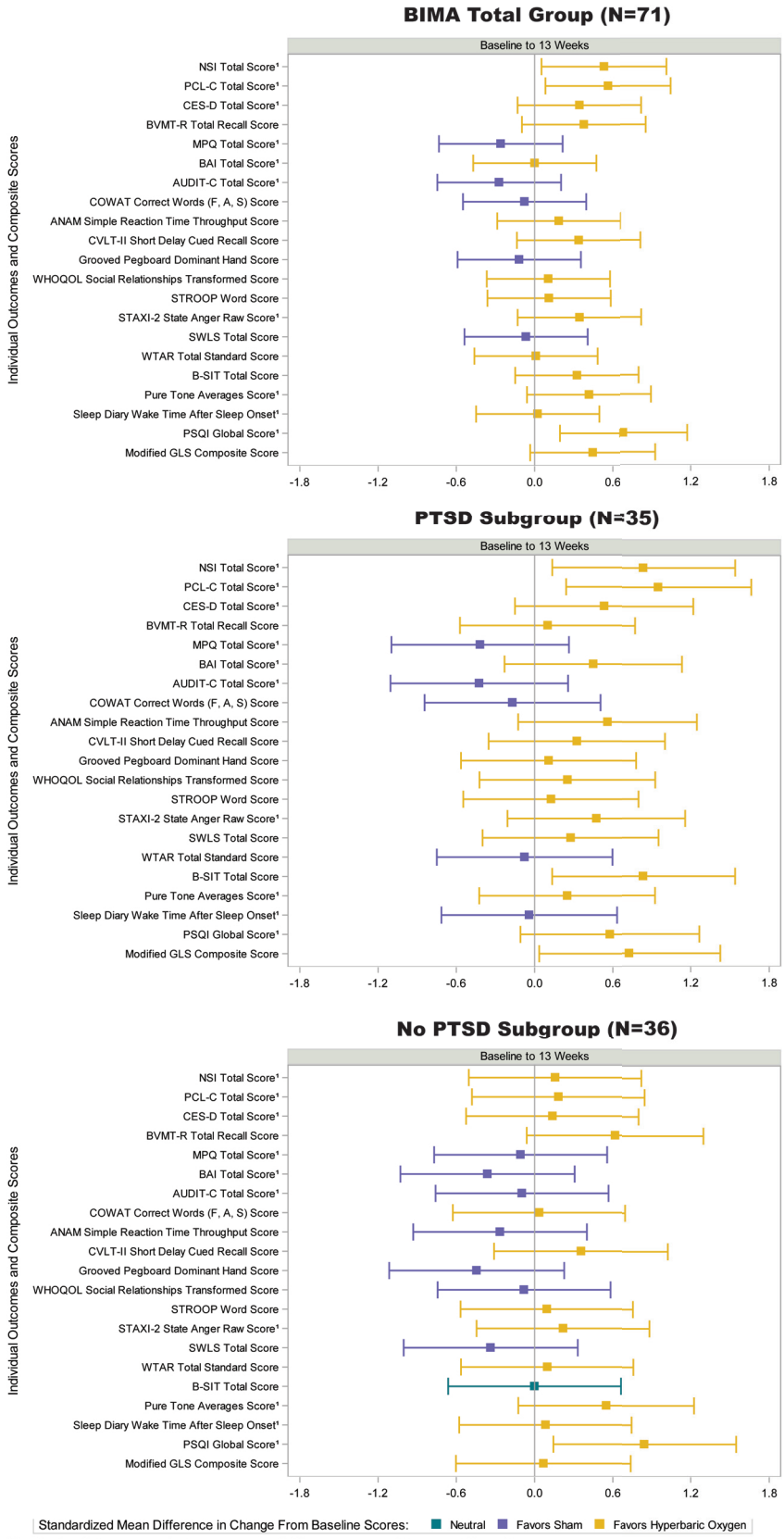
Most baseline characteristics were balanced between intervention groups. The few notable imbalances included older age, more deployments, worse anger control, and more frequent evidence of diffuse/traumatic axonal injury in the HBO_2 group compared to sham. Although proper randomization can ensure that baseline differences between groups are due to chance rather than bias, it does not guarantee that groups will be well-matched [30]. Differences in baseline characteristics may be important when they represent an outcome measure of interest or are considered prognostic. In the case of mild TBI, older patients may be at greater risks for development of post-concussive symptoms [31], and white matter changes may be associated with the severity of those symptoms [32]. In addition, the HBO_2 group in BIMA performed worse at baseline on a few of the outcome measures. These baseline differences were not found to be significant when adjusted for in additional exploratory models of intervention effect. Longitudinal modeling showed benefit with HBO_2 on post-concussive and PTSD symptoms. In another U.S. military study, participants randomized

TABLE 10. Results of subgroup analyses

	Subgroup analysis: age[a]						Subgroup analysis: trauma type[b]					
	≤32 years (n=37) (hyperbaric oxygen n=15, sham n=22)			>32 years (n=34) (hyperbaric oxygen n=21, sham n=13)			Blunt force trauma only (n=14) (hyperbaric oxygen n=7, sham n=7)			At least 1 blast injury (n=57) (hyperbaric oxygen n=29, sham n=28)		
Characteristics	Baseline	13-week change	Difference mean (SD) [95% CI] p-value	Baseline	13-week change	Difference mean (SD) [95% CI] p-value	Baseline	13-week change	Difference mean (SD) [95% CI] p-value	Baseline	13-week change	Difference mean (SD) [95% CI] p-value
Neurobehavioral Symptom Inventory												
Total score												
Hyperbaric oxygen	30.4 (10.7)	-4.1 (9.2)	-11.0 (11.5) [-18.9, -3.1] 0.008	40.3 (14.6)	-3.3 (19.8)	-2.0 (16.6) [-14.2, 10.3] 0.75	35.7 (13.2)	3.1 (10.7)	2.1 (11.5) [-11.9, 16.2] 0.74	36.3 (14.3)	-5.2 (16.9)	-9.8 (14.7) [-17.7, -2.0) 0.02
Sham	30.7 (16.2)	7.0 (12.8)		31.4 (12.7)	-1.3 (8.1)		34.3 (19.6)	1.0 (12.3)		30.1 (13.6)	4.6 (12.0)	
Affective domain												
Hyperbaric oxygen	13.2 (4.7)	-2.2 (4.3)	-4.1 (4.6) [-7.2, -0.9] 0.01	16.4 (5.6)	-1.9 (7.5)	-2.1 (6.5) [-6.9, 2.7] 0.38	15.4 (5.7)	1.1 (2.4)	0.8 (3.7) [-3.8, 5.4] 0.70	15.0 (5.5)	-2.8 (6.7)	-4.2 (5.8) [-7.3, -1.1] 0.008
Sham	12.9 (6.3)	1.9 (4.9)		12.2 (5.2)	0.2 (4.2)		13.4 (8.5)	0.3 (4.8)		12.4 (5.2)	1.4 (4.7)	
Somatic domain												
Hyperbaric oxygen	10.1 (5.2)	-1.3 (3.6)	-5.2 (5.6) [-9.0, -1.4] 0.009	14.7 (6.5)	-0.4 (8.9)	1.5 (7.7) [-4.2, 7.3] 0.59	12.7 (7.3)	0.1 (5.3) -0.2 (6.6)	0.3 (5.9) [-7.0, 7.6] 0.93	12.8 (6.3)	-1.0 (7.5)	-3.2 (7.1) [-7.0, 0.6] 0.10
Sham	10.2 (7.3)	3.9 (6.6)		12.2 (6.3)	-1.9 (5.1)		12.1 (8.2)			10.6 (6.6)	2.2 (6.7)	
Cognitive domain												
Hyperbaric oxygen	7.1 (3.7)	-0.5 (3.2)	-1.8 (3.3) [-4.1, 0.5] 0.13	9.2 (4.1)	-1.0 (4.7)	-1.4 (4.1) [-4.4, 1.6] 0.35	7.6 (3.9)	1.9 (3.7)	1.0 (4.1) [-4.0, 6.1] 0.66	8.5 (4.1)	-1.4 (4.0)	-2.4 (3.5) [-4.3, -0.5] 0.01
Sham	7.6 (4.2)	1.2 (3.4)		7.1 (3.2)	0.4 (2.7)		8.7 (4.6)	0.8 (4.6)		7.1 (3.6)	1.0 (2.9)	
Rivermead Post-Concussion Symptom Questionnaire												
RPQ-3												
Hyperbaric oxygen	5.5 (2.9)	-1.5 (1.7)	-2.9 (2.0) [-4.2, -1.5] <0.001	6.0 (2.9)	0.5 (3.0)	-0.4 (2.9) [-2.5, 1.7] 0.71	7.0 (2.4)	-0.6 (2.0)	-1.9 (2.1) [-4.5, 0.7] 0.13	5.5 (2.9)	-0.3 (2.9)	-1.4 (2.6) [-2.8, -0.0] 0.05
Sham	4.5 (2.9)	1.3 (2.1)		4.5 (2.2)	0.9 (2.5)		5.6 (4.2)	1.3 (2.3)		4.3 (2.1)	1.1 (2.3)	
RPQ-13												
Hyperbaric oxygen	26.0 (9.9)	-3.6 (6.4)	-10.8 (9.4) [-17.2, -4.4] 0.002	31.2 (11.4)	2.0 (15.0)	1.7 (13.5) [-8.3, 11.7] 0.73	28.7 (10.0)	-0.7 (10.4)	-9.2 (10.9) [-22.5, 4.1] 0.16	29.1 (11.4)	-0.3 (12.9)	-4.1 (12.1) [-10.6, 2.4] 0.21
Sham	23.1 (11.0)	7.2 (11.0)		24.5 (12.5)	0.3 (10.3)		24.0 (17.5)	8.5 (11.5)		23.6 (9.8)	3.8 (11.1)	
Post-Traumatic Stress Disorder Checklist-Civilian Version												
Total score												
Hyperbaric oxygen	39.7 (8.8)	-3.8 (11.7)	-7.7 (10.0) [-14.5, -0.9] 0.03	51.3 (14.7)	-4.5 (19.0)	-6.1 (16.0) [-17.9, 5.7] 0.30	45.3 (13.2)	-2.1 (10.8)	-3.0 (9.9) [-15.1, 9.2] 0.60	46.8 (14.0)	-4.7 (17.3)	-8.2 (13.7) [-15.6, -0.9] 0.03
Sham	44.4 (15.1)	3.9 (8.6)		41.3 (12.1)	1.6 (8.2)		44.1 (20.0)	0.8 (8.8)		43.0 (12.5)	3.6 (8.4)	
Re-experiencing score												
Hyperbaric oxygen	10.1 (4.1)	-0.3 (5.3)	-1.5 (4.4) [-4.6, 1.5] 0.31	14.2 (5.1)	-1.7 (6.7)	-2.2 (5.6) [-6.4, 2.0] 0.29	11.0 (5.7)	0.6 (6.3)	0.7 (5.2) [-5.6, 7.1] 0.80	12.9 (5.0)	-1.6 (6.1)	-2.7 (5.0) [-5.4, -0.1] 0.04
Sham	12.4 (4.5)	1.2 (3.6)		11.3 (4.4)	0.5 (3.0)		11.6 (6.1)	-0.2 (3.4)		12.1 (4.1)	1.2 (3.4)	
Avoidance/numbing score												
Hyperbaric oxygen	13.9 (4.7)	-1.1 (4.9)	-2.6 (4.2) [-5.5, 0.3] 0.07	18.7 (7.4)	-0.8 (8.1)	-1.8 (6.9) [-6.9, 3.3] 0.47	17.1 (7.5)	-0.6 (4.5)	0.1 (3.9) [-4.7, 4.8] 0.97	16.6 (6.7)	-1.0 (7.4)	-2.8 (5.9) [-6.0, 0.4) 0.08
Sham	16.7 (7.5)	1.6 (3.6)		15.6 (5.0)	1.0 (3.7)		18.1 (9.2)	-0.7 (2.9)		15.8 (6.0)	1.8 (3.6)	
Hyperarousal score												
Hyperbaric oxygen	15.7 (3.1)	-2.4 (3.7)	-3.5 (3.5) [-5.9, -1.2] 0.005	18.4 (3.9)	-2.0 (5.6)	-2.0 (4.8) [-5.6, 1.5] 0.25	17.1 (3.4)	-2.1 (3.8)	-3.8 (3.6) [-8.2, 0.6] 0.08	17.3 (3.9)	-2.1 (5.1)	-2.7 (4.3) [-5.0, -0.4] 0.02
Sham	15.3 (4.7)	1.1 (3.4)		14.4 (4.2)	0.1 (3.0)		14.4 (5.9)	1.7 (3.3)		15.1 (4.2)	0.6 (3.2)	

[a] Age by intervention interaction P-values respectively, for Neurobehavioral Symptom Inventory Total, Affective, Somatic, and Cognitive scores: 0.20, 0.48, 0.05, and 0.85; for RPQ-3 and RPQ-13: 0.04 and 0.03; for Post-Traumatic Stress Disorder Checklist-Civilian Version Total, Re-experiencing, Avoidance/numbing, and Hyperarousal scores: 0.80, 0.78, 0.77, and 0.47.

[b] Trauma type by intervention interaction P-values respectively, for Neurobehavioral Symptom Inventory Total, Affective, Somatic, and Cognitive scores: 0.18, 0.14, 0.42, and 0.13; for RPQ-3 and RPQ-13: 0.76 and 0.49; for Post-Traumatic Stress Disorder Checklist-Civilian Version Total, Re-experiencing, Avoidance/numbing, and Hyperarousal scores: 0.52, 0.27, 0.40, and 0.67.



¹The direction of change scores has been reversed so that increases represent improvement in symptoms.

FIGURE 5. Forest plots of composite scores . . .

and their components via global statistical tests for multiple outcomes for the BIMA total population and the PTSD and no-PTSD subgroups. Where possible, components taken as total outcome scores of neuropsychological, neurological function, vestibular and auditory, and sleep assessments. For assessments with many outcomes and without a total score measure, preference given to outcomes with fewest missing values and to those with point estimates (effect size) close to the median estimate across all effect sizes for that instrument. The standardized mean intervention-difference in change from baseline scores to 13 weeks and 95% confidence intervals for modified Generalized Least Squares statistics and components are presented. Greater weights are placed on outcomes that are less correlated with other measures in the composite scores via modified Generalized Least Squares.

Abbreviations: NSI, Neurobehavioral Symptom Inventory; PCL-C, Post-Traumatic Stress Disorder Checklist – Civilian version; CES-D, Centers for Epidemiological Studies – Depression scale; BVMT-R, Brief Visuospatial Memory Test – Revised; MPQ, McGill Pain Questionnaire; BAI, Beck Anxiety Inventory; AUDIT-C, Alcohol Use Disorders Identification Test; COWAT, Controlled Oral Word Association Test; ANAM, Automated Neuropsychological Assessment Metrics; CVLT-II, California Verbal Learning Test – Second Edition; WHOQOL, World Health Organization Quality of Life; STAXI-2, State-Trait Anger Expression Inventory – 2; SWLS, Satisfaction with Life Scale; WTAR, Wechsler Test of Adult Read; B-SIT, Brief Smell Identification Test; PSQI, Pittsburgh Sleep Quality Index; GLS, Generalized Least Squares

to local care worsened over 13 weeks [11], suggesting post-concussive symptoms are unlikely to improve without intervention during that interval.

BIMA did not utilize a symptom validity questionnaire. However, despite secondary gain concerns, validity components of neuropsychological, neurological and vestibular evaluations showed no evidence of malingering. Lack of general improvement in both arms suggests test-retest phenomena did not drive study results. However, if the changes observed in the HBO_2 arm represent "treatment" of post-concussive symptoms after mild TBI, the wide confidence intervals of the point estimates indicate uncertainty about the degree of clinical effect of HBO_2 in this population. With a larger sample size, the confidence intervals would provide a better estimate of change, from which one could determine whether clinically important improvement could be expected. Nevertheless, BIMA participant responses to the Patient Global Impression of Change questionnaire suggest that the improvements they reported were of clinical significance to them.

BIMA is the fourth U.S. military randomized trial studying HBO_2 for post-concussive symptoms [10-12]. Two of these studies reported improvement with HBO_2 and sham [11,12]; another found PTSD improvement with 2.0 ATA HBO_2 [10]. Design differences may explain discrepant study results [9] (Table 11). The intervention groups in BIMA were approximately 40% larger than in any of the prior studies. Compared to the prior studies, BIMA's participants were older and had more education. Two prior studies used different sham and intervention chamber pressures/durations (2.4 ATA oxygen, 1.3 ATA air, 110 minutes [12]; 2.0 ATA, 60 minutes, three inhaled oxygen concentrations [9,10], which may not be clinically equivalent to the chamber sessions used in BIMA.

One study [11] used HBO_2 and sham interventions identical to BIMA, but participants in that study improved with both interventions, perhaps due to dissimilar outcome measures, populations, sites, and protocol adherence. This prior study [11] enrolled more sham participants with PTSD (64% vs. BIMA's 49%), and fewer completed 40 sessions (49% vs. BIMA's 83%). BIMA's travel requirements and extensive evaluations may have introduced selection bias: the prior study enrolled 27% of screened individuals, while BIMA enrolled 17%.

Blinding of participants to intervention is imperative in clinical trials, especially in trials whose outcomes include participant reports. Participants in HBO_2 trials must experience pressure equalization in their middle ears to preserve the blind. Investigators in these two trials chose the lowest pressure felt necessary to maintain the blind and minimize potential biological effects on the human central nervous system [33]. The identical shams used in these two studies exposed participants to increased partial pressures of oxygen and nitrogen: The increase in oxygen partial pressure is equivalent to breathing oxygen by nasal cannula at 1 liter per minute at atmospheric pressure, and the increase in nitrogen partial pressure is equivalent to breathing air while submerged to a depth of 6.6 feet of sea water.

Some have expressed concern that the sham exposures used in BIMA have biologic effect of therapeutic importance [34], but that evidence is sparse [28,33], and in the BIMA trial, the sham group had worsened symptoms at 13 weeks. None of the military trials were designed to investigate whether their sham exposures offer advantage to post-concussive symptoms. Whether the associated sham exposures have a therapeutic effect on the chronically damaged human brain (an outcome that was not observed in BIMA) is not known. Future clinical trials could be designed to investigate therapeutic properties of low pressure air "sham" hyperbaric exposures in brain-injured individuals.

No prior study reported outcomes beyond six months except in a low-enrolling follow-on project [35]. BIMA followed participants to 12 months with high retention and compliance. Other study strengths include comprehensive outcome assessments, federally compliant data management, and a single assessment center with consistent equipment and evaluators.

BIMA was an exploratory, Phase II study; accordingly, conclusions about efficacy cannot be drawn. Other study limitations include sample size, testing a single HBO_2 dose/pressure/frequency, a potentially non-inert sham, frequent concomitant PTSD, remote follow-up at 12 months, and potential TBI severity imbalance between groups. Given the relatively small sample size, heterogeneity, polypharmacy, multiplicity, among other factors, the signal-to-noise ratio favoring HBO_2 must have been sufficiently large to overcome these substantial confounds in this population in order to demonstrate an intervention effect.

Favorable effects of HBO_2 decreased over time, and both BIMA groups reported statistically non-significant worsened symptoms at 12 months. This lack of change

TABLE 11. Comparison of military studies

	U.S. Air Force 2[12, 80-82]	U.S. Navy/VCU [10, 35, 83-85]	U.S. Army: HOPPS [11, 35]	U.S. Army: BIMA [13]
Study Arms	HBO_2 (n=25) (2.4 ATA, >99% O_2) Sham (n=25) (1.3 to 1.2 ATA, air)	HBO_2 2.0 equivalent (n=21) (2.0 ATA, >99% O_2) HBO_2 2.0 equivalent (n=21) (2.0 ATA, 75% O_2) Sham (n=18) (2.0 ATA, 10.5% O_2)	HBO_2 (n=24) (1.5 ATA, >99% O_2) Sham (n=25) (1.2 ATA, air) Local care (n=23) (no intervention)	HBO_2 (n=36) (1.5 ATA, >99% O_2) Sham (n=35) (1.2 ATA, air)
Sessions	30 sessions 90 minutes at pressure	40 sessions 60 minutes door to door	40 sessions 60 minutes door to door	40 sessions 60 minutes door to door
Sites	Brooks City-Base, Texas Recruited from Camp Lejeune, North Carolina, 29 Palms, California, and other military installations	Naval Air Station, Pensacola, Florida Recruited from Camp Lejeune, North Carolina, and Quantico, Virginia	Fort Carson, Colorado Camp Lejeune, North Carolina Camp Pendleton, California Fort Gordon, Georgia	Fort Carson, Colorado Camp Lejeune, North Carolina Joint Base Lewis-McChord, Washington
Participants	Mean age 28 years 48 males Mean education 12 years Mean 3.4 prior concussions 33 blast 8 blunt force 9 blast and blunt force PTSD rate 50%	Mean age 23 years 60 males Education not reported 25% had >1 concussion All had at least 1 blast injury	Median age 31 years 69 males 66% had some college or more Mean 3 lifetime concussions 51 had blast injury as their most recent injury PTSD rate 66%	Mean age 33 years 70 males 82% had some college or more Mean 3.6 prior concussions 23 blast 14 blunt force 34 blast and blunt force PTSD rate 49%
Qualifying injury	Neurologist-confirmed TBI diagnosis >3 months from injury 3 participants had >mild TBI	TBI-specialist confirmed diagnosis >3 months from injury	Structured interview >4 months from injury	Structured interview >3 months from injury
Head injuries during participation	Not reported	Not reported	2 participants had an additional mild TBI (over 13 weeks)	5 participants had an additional mild TBI (over 12 months)
Outcome Assessments	IMPACT, PCL-M before, weekly, and after chamber sessions	RPQ, PCL-M, eye tracking, cognitive, and balance measures before and after chamber sessions and 3 months later.	Post-concussive symptoms, quality of life, neuropsychological testing before and after chamber sessions.	Comprehensive outcome assessments at baseline, 13 weeks, and 6 months. Questionnaires at 12 months.
Travel requirement	2-month relocation for chamber sessions and testing	2-month relocation for chamber sessions	None	Travel to Colorado Springs, Colorado at baseline, 13 weeks, and 6 months for assessments.
Compliance	Not reported	All received intervention as assigned.	24/49 (49%) assigned to chamber sessions received 40 sessions. 34/49 (69%) received ≥30 sessions. 3 sham participants did not complete any chamber sessions.	59/71 (83%) completed 40 sessions (see Figure 2).
Analysis	Not reported	Per protocol. 60/61 included in primary analysis. 10 participants excluded from cognitive performance analysis due to failed validity testing.	Intent-to-treat	Intent-to-treat
Key Results	Both HBO_2 and sham arms had improvement in IMPACT symptoms and cognitive performance and PTSD symptoms. Subgroup with PTSD had better response with HBO_2 on PCL-M. No significant differences on IMPACT.	No significant within-group changes on RPQ, cognitive function, or balance. No clinical improvements with eye tracking. Significant improvement on PCL-M with HBO_2 2.0 ATA.	Worsening or no change on measures in local care group. Sham and HBO_2 groups had significant within-group improvements but no between-group differences.	Improvements in post-concussive and PTSD symptoms, sleeps, and anger control with HBO_2, not sham. Greatest at 13 weeks and in the subset with PTSD. Few changes in other outcomes.

durability could be due to an insufficient number of HBO_2 sessions (i.e., underdosing). A trial of 40 sessions was selected based on expert consensus as a dose that might show an effect, not one intended to demonstrate maximal improvement. In this population, comorbidities (e.g., PTSD, medications, additional injuries) and common life stressors (e.g., deployments, transition from the military, interpersonal conflicts, grief and loss) could have worsened post-concussive symptoms over time. Many of these symptoms are not specific to mild TBI. Based on the observed changes in the non-intervention local care group in another study [11], the natural course of mild TBI may include worsening symptoms. Alternatively, participants may have returned to baseline but reported worsened symptoms in the context of earlier improvement and waning treatment effects.

Results from BIMA and other military trials may not extrapolate to civilians. Injury etiology (blunt force trauma vs. blast), medical management of symptoms, and prevalence of concomitant PTSD differ significantly between these populations. However, a civilian non-sham-controlled randomized trial in mild TBI demonstrated improvements with HBO_2 profiles similar to BIMA's [7].

Should military personnel with persistent post-concussive symptoms following mild TBI receive HBO_2? Hyperbaric oxygen is well tolerated but expensive, inconvenient, and not universally available. In all four military-sponsored studies, participants exposed to HBO_2 reported symptom improvement. In two trials, participants exposed to sham also improved. The magnitude of improvement in self-reported assessments by 13 weeks is larger than any non-hyperbaric intervention previously reported [36]. Many questions remain about efficacy, effectiveness, dosing, patient selection, timing and mechanisms.

Results from BIMA suggest that HBO_2 may have a favorable effect that merits further study in service members, especially in those with PTSD. A dose-response investigation or study of PTSD without TBI would be of value, and a no-pressure sham arm could resolve questions about any biological effect of the sham pressures used in BIMA and prior military studies. Based on BIMA results, the NSI would be a reasonable, simple primary outcome measure in future studies. Secondary outcome measures might include a PTSD measure, a sleep questionnaire, the Patient Global Impression of Change, and the limited quality of life and neuropsychological tests included in the modified GLS composite measure presented here; the more resource-intensive measures included in BIMA did not prove useful for measuring change in this population. Once an optimal dose of HBO_2 is established, we recommend the conduct of an adequately powered Phase III efficacy study before HBO_2 is considered for adoption as a standard of care treatment for persistent post-concussive symptoms after mild TBI.

■

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The BIMA trial was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki. In the conduct of research where humans are the subjects, the investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects). The BIMA study was approved by the United States Army Medical Research and Materiel Command Institutional Review Board; written informed consent was obtained for all participants prior to administering study assessments. The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

All the authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of the trial to the protocol. SHW and ASL performed the data analysis. Other authors participated in data analyses within in their respective subject matter expertise. LKW and KD prepared the first draft of the manuscript. All authors participated in the writing of the manuscript and approved the draft that was submitted for publication. The results were reviewed by the Sponsor.

REFERENCES

1. Zaloshnja E, Miller T, Langlois JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil. 2008 Nov-Dec;23(6):394-400.

2. The CDC, NIH, DoD, and VA Leadership Panel. Report to Congress on traumatic brain injury in the United States: understanding the public health problem among current and former military personnel: Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Department of Defense (DoD), and the Department of Veterans Affairs (VA); 2013.

3. Terrio H, Brenner LA, Ivins BJ, et al. Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. J Head Trauma Rehabil. 2009 Jan-Feb;24(1):14-23.

4. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. Am J Epidemiol. 2008 Jun 15;167(12):1446-1452.

5. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. J Neurotrauma. 2010 Aug;27(8):1529-1540.

6. Harch PG, Andrews SR, Fogarty EF, et al. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma. 2012 Jan 1;29(1):168-185.

7. Boussi-Gross R, Golan H, Fishlev G, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. PLoS One. 2013;8(11):e79995.

8. McCrary BF, Weaver LK, Marrs K, et al. Hyperbaric oxygen (HBO_2) for post-concussive syndrome/chronic TBI: product summary. Undersea Hyperb Med. 2013;40(5):443-467.

9. Weaver LK, Cifu D, Hart B, Wolf G, Miller S. Hyperbaric oxygen for post-concussion syndrome: design of Department of Defense clinical trials. Undersea Hyperb Med. 2012 Jul-Aug;39(4):807-814.

10. Cifu DX, Hart BB, West SL, Walker W, Carne W. The effect of hyperbaric oxygen on persistent postconcussion symptoms. J Head Trauma Rehabil. 2014 Jan-Feb;29(1):11-20.

11. Miller RS, Weaver LK, Bahraini N, et al. Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. JAMA Intern Med. 2015 Jan;175(1):43-52.

12. Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. J Neurotrauma. 2012 Nov 20;29(17):2606-2612.

13. Weaver LK, Chhoeu AH, Lindblad AS, Churchill S, Wilson SH. Hyperbaric oxygen for mild traumatic brain injury: design and baseline summary. Undersea Hyperb Med. 2016;43(5):489-508.

14. Corrigan JD, Bogner J. Initial reliability and validity of the Ohio State University TBI Identification Method. J Head Trauma Rehabil. 2007 Nov-Dec;22(6):318-329.

15. Casscells SW. Traumatic brain injury: definition and reporting. Memorandum. Washington, DC: Assistant Secretary of Defense for Health Affairs; 2007.

16. Ramirez Basco M, Bostic JQ, Davies D, et al. Methods to improve diagnostic accuracy in a community mental health setting. Am J Psychiatry. 2000 Oct;157(10):1599-1605.

17. Williams CS, Weaver LK, Lindblad AS, Kumar S, Langford DR. Baseline neurological evaluations in a hyperbaric trial of post-concussive syndrome. Undersea Hyperb Med. 2016;43(5):511-519.

18. Williams CS, Spitz MC, Foley JF, Weaver LK, Lindblad AS, Wierzbicki MR. Baseline EEG abnormailities in mild traumatic brain injury from the BIMA study. Undersea Hyperb Med. 2016;43(5): 521-530.

19. Mirow S, Wilson SH, Weaver LK, Churchill S, Deru K, Lindblad AS. Linear analysis of heart rate variability in post-concussive syndrome. Undersea Hyperb Med. 2016;43:531-547.

20. Walker JM, James NT, Campbell H, Wilson SH, Churchill S, Weaver LK. Sleep assessments for a mild traumatic brain injury trial in a military population. Undersea Hyperb Med. 2016;43(5):549-566.

21. Meehan A, Searing E, Weaver LK, Lewandowski A. Baseline vestibular and auditory findings in a trial of post-concussive syndrome. Undersea Hyperb Med. 2016;43(5):567-584.

22. Wilson SH, Weaver LK, Lindblad AS. Neuropsychological assessments in a hyperbaric trial of post-concussive symptoms. Undersea Hyperb Med. 2016;43(5):585-599.

23. Tang DI, Geller NL, Pocock SJ. On the design and analysis of randomized clinical trials with multiple endpoints. Biometrics. 1993 Mar;49(1):23-30.

24. Eyres S, Carey A, Gilworth G, Neumann V, Tennant A. Construct validity and reliability of the Rivermead Post-Concussion Symptoms Questionnaire. Clin Rehabil. 2005 Dec;19(8):878-887.

25. Orrison WW, Hanson EH, Alamo T, et al. Traumatic brain injury: a review and high-field MRI findings in 100 unarmed combatants using a literature-based checklist approach. J Neurotrauma. 2009 May;26(5):689-701.

26. Shandley S, Wolf EG, Schubert-Kabban C, et al. Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy. Undersea Hyperb Med. 2017;44(3):257-269.

27. Hoge CW, Jonas WB. The ritual of hyperbaric oxygen and lessons for the treatment of persistent postconcussion symptoms in military personnel. JAMA Intern Med. 2015 Jan;175(1):53-54.

28. Mitchell SJ, Bennett MH. Unestablished indications for hyperbaric oxygen therapy. Diving Hyperb Med. 2014 Dec;44(4):228-234.

29. Figueroa XA, Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. Neurology. 2016 Sep 27; 87(13):1400-1406.

30. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 23;340:c869.

31. King N. Permanent post concussion symptoms after mild head injury: a systematic review of age and gender factors. NeuroRehabilitation. 2014;34(4):741-748.

32. Smits M, Houston GC, Dippel DW, et al. Microstructural brain injury in post-concussion syndrome after minor head injury. Neuroradiology. 2011 Aug;53(8):553-563.

33. Weaver LK, Cifu D, Hart B, Wolf G, Miller RS. Reply: Department of Defense trials for hyperbaric oxygen and TBI: issues of study design and questionable conclusions. Undersea Hyperb Med. 2013 Sep-Oct; 40(5):471-472.

34. Harch PG. Department of Defense trials for hyperbaric oxygen and TBI: issues of study design and questionable conclusions. Undersea Hyperb Med. 2013;40(5):469-470.

35. Skipper LD, Churchill S, Wilson SH, Deru K, Labutta RJ, Hart BB. Hyperbaric oxygen for persistent post-concussive symptoms: long-term follow-up. Undersea Hyperb Med. 2016;43(5):601-613.

36. Wilson SH, Rothe M, Lindblad AS, Weaver LK. Review of recent non-hyperbaric oxygen interventions for mild traumatic brain injury. Undersea Hyperb Med. 2016;43(5):615-627.

37. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. J Neurosurg. 1987 Feb;66(2):234-243.

38. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. J Neurol. 1995 Sep;242(9):587-592.

39. Grieger TA, Cozza SJ, Ursano RJ, et al. Posttraumatic stress disorder and depression in battle-injured soldiers. Am J Psychiatry. 2006 Oct;163(10):1777-1783; quiz 1860.

40. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas. 1977 June 1, 1977;1(3):385-401.

41. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988 Dec;56(6):893-897.

42. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998 Sep 14;158(16):1789-1795.

43. Guilfoyle MR, Seeley HM, Corteen E, et al. Assessing quality of life after traumatic brain injury: examination of the short form 36 health survey. J Neurotrauma. 2010 Dec;27(12):2173-2181.

44. Chiu WT, Huang SJ, Hwang HF, et al. Use of the WHOQOL-BREF for evaluating persons with traumatic brain injury. J Neurotrauma. 2006 Nov;23(11):1609-1620.

45. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. J Pers Assess. 1985 Feb;49(1):71-75.

46. Flaherty SA. Pain measurement tools for clinical practice and research. AANA J. 1996 Apr;64(2):133-140.

47. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther. 2004 Jan;27(1):26-35.

48. Kabat MH, Kane RL, Jefferson AL, DiPino RK. Construct validity of selected Automated Neuropsychological Assessment Metrics (ANAM) battery measures. Clin Neuropsychol. 2001 Dec;15(4):498-507.

49. Becker S, Lim J. A computational model of prefrontal control in free recall: strategic memory use in the California Verbal Learning Task. J Cogn Neurosci. 2003 Aug 15;15(6):821-832.

50. Benedict RHB, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity1996. 145-153 p.

51. Tombaugh TN. The Test of Memory Malingering (TOMM): normative data from cognitively intact and cognitively impaired individuals. Psychol Assess. 1997;9(3):260-268.

52. Wechsler D. Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV). San Antonio, TX: Pearson Assessments; 2008.

53. Wechsler D. Wechsler Test of Adult Reading (WTAR). San Antonio, TX: Psychological Corporation; 2001.

54. Golden CJ. A manual for the Stroop Color and Word Test. Chicago, IL: Stoelting Co.; 1978.

55. Ruff RM, Light RH, Parker SB, Levin HS. Benton Controlled Oral Word Association Test: reliability and updated norms. Arch Clin Neuropsychol. 1996;11(4):329-338.

56. Ruffolo LF, Guilmette TJ, Willis GW. Comparison of time and error rates on the trail making test among patients with head injuries, experimental malingerers, patients with suspect effort on testing, and normal controls. Clin Neuropsychol. 2000 May;14(2):223-230.

57. Hanna-Pladdy B, Mendoza JE, Apostolos GT, Heilman KM. Lateralised motor control: hemispheric damage and the loss of deftness. J Neurol Neurosurg Psychiatry. 2002 Nov;73(5):574-577.

58. Bishop GD, Quah S. Reliability and validity of measures of anger/hostility in Singapore: Cook & Medley Ho Scale, STAXI and Buss-Durkee Hostility Inventory. 1998;24:867-878.

59. Lee CT. Sharpening the Sharpened Romberg. SPUMS J. 1998 Sep; 28(3):125-132.

60. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope. 1996 Mar; 106(3 Pt 1):353-356.

61. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring-balance in the elderly: validation of an instrument. Can J Public Health. 1992 Jul-Aug;83 Suppl 2:S7-11.

62. Edwards RH, Hyde S. Methods of measuring muscle strength and fatigue. Physiotherapy. 1977 Feb;63(2):51-55.

63. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 01;166(1):111-117.

64. Chung F, Yang Y, Brown R, Liao P. Alternative scoring models of STOP-bang questionnaire improve specificity to detect undiagnosed obstructive sleep apnea. J Clin Sleep Med. 2014;10(9):951-958.

65. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193-213.

66. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003 May 1;26(3):342-392.

67. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep. 2007 Apr;30(4):519-529.

68. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology. 1973 Jul;10(4):431-436.

69. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003 Mar;4(2):101-119. Epub 2003/11/01. eng.

70. Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. Sleep. 1999 Feb 01;22(1):77-87.

71. O'Leary DP, Davis LL. High-frequency autorotational testing of the vestibulo-ocular reflex. Neurol Clin. 1990 May;8(2):297-312.

72. Balance function assessment and management. San Diego: Plural Publishing; 2008.

73. Hirvonen TP, Aalto H, Pyykko I, Juhola M. Comparison of two head autorotation tests. J Vestib Res. 1999;9(2):119-125.

74. Felipe L, Kingma H. Ocular vestibular evoked myogenic potentials. Int Arch Otorhinolaryngol. 2014 Jan;18(1):77-79.

75. Badke MB, Shea TA, Miedaner JA, Grove CR. Outcomes after rehabilitation for adults with balance dysfunction. Arch Phys Med Rehabil. 2004 Feb;85(2):227-233.

76. Kothari MT, Venkatesan G, Shah JP, Kothari K, Nirmalan PK. Can ocular torsion be measured using the slitlamp biomicroscope? Indian J Ophthalmol. 2005 Mar;53(1):43-47.

77. Clark JF, Ellis JK, Burns TM, Childress JM, Divine JG. Analysis of Central and Peripheral Vision Reaction Times in Patients With Postconcussion Visual Dysfunction. Clin J Sport Med. 2017 Sep; 27(5):457-461.

78. Cifu DX, Wares JR, Hoke KW, Wetzel PA, Gitchel G, Carne W. Differential eye movements in mild traumatic brain injury versus normal controls. J Head Trauma Rehabil. 2015 Jan-Feb;30(1):21-28.

79. Furman JM. Role of posturography in the management of vestibular patients. Otolaryngol Head Neck Surg. 1995 Jan;112(1): 8-15.

80. Wolf EG, Baugh LM, Kabban CM, Richards MF, Prye J. Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial. Undersea Hyperb Med. 2015 Jul-Aug;42(4):313-332.

81. Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. Undersea Hyperb Med. 2012 Nov-Dec;39(6):1075-1082.

82. Scorza KA, McCarthy W, Miller RS, Carne W, Wolf EG. Hyperbaric oxygen effects on PTSD and mTBI symptoms: a subset analysis. Undersea Hyperb Med. 2013;40(6):548.

83. Cifu DX, Walker WC, West SL, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: three-month outcomes. Ann Neurol. 2014 Feb;75(2):277-286.

84. Walker WC, Franke LM, Cifu DX, Hart BB. Randomized, Sham-Controlled, Feasibility Trial of Hyperbaric Oxygen for Service Members With Postconcussion Syndrome: Cognitive and Psychomotor Outcomes 1 Week Postintervention. Neurorehabil Neural Repair. 2014;28(5): 420-432.

85. Cifu DX, Hoke KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effects of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. J Rehabil Res Dev. 2014;51(7): 1047-1056.

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