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A double-blind randomized trial of hyperbaric oxygen for persistent symptoms after brain injury

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In this double-blind randomized trial, adults with persistent symptoms following non-stroke brain injury received 40 hyperbaric oxygen (HBO_2) sessions or 40 sham sessions over 12 weeks. Three months later, all were offered 40 unblinded HBO_2 sessions. Participants completed the Neurobehavioral Symptom Inventory (NSI) at baseline, 13 weeks (after 40 chamber sessions), 6 months, 9 months (after the second chamber series), and 12 months, with prime outcome at 13 weeks, and additional questionnaires, neuropsychological tests, and functional measures. We enrolled 49 participants and analyzed 47 due to drop-out/exclusion (26 males, 40 with traumatic brain injury). Baseline NSI was 35.9 ± 15.8 in the HBO_2 group ($n = 26$) and 30.7 ± 16.9 in the sham group ($n = 21$) ($p = 0.28$). Mean 13-week change scores were 10.6 ± 10.6 (HBO_2 group) and 3.6 ± 5.9 (sham group) (mean difference 7.0, 95% CI 1.7–12.3, $p = 0.01$). The HBO_2 group improved on measures of olfaction, anxiety, sleep difficulties, and vestibular complaints. Both groups reported improvements in depression, headaches, PTSD symptoms, physical quality of life, and degree to which difficulties interfere with daily life. With an additional 40 HBO_2 sessions, the original HBO_2 group reported additional improvements on NSI at 12 months. Only 15 original sham participants completed the second chamber series, limiting conclusions from that data.

Keywords Hyperbaric oxygen, Randomized trial, Brain injury, Traumatic brain injury, Carbon monoxide poisoning, Blinded

Brain injury occurs from many etiologies, including trauma, stroke, hypoxia, infection, inflammation, nutritional deficiencies, post-COVID-19 (SARS-CoV-2) condition, or toxic exposures, and can result in functional deficits and persistent symptoms that impact quality of life. Millions in the United States suffer a brain injury each year[1–3], and many continue to suffer from persistent brain injury symptoms[3–8] that can encompass cognitive, affective, neurological, somatic[9,10], and cardiac[11–13] domains. Common complaints are headache, cognitive deficits, sleep disturbances, dizziness, post-traumatic stress disorder (PTSD), and behavioral and affective changes[10,14]. Persistent symptoms can interfere with work performance, independent living, and psychosocial function. No curative intervention has yet been widely accepted or endorsed for these brain injury problems. Treatment generally focuses on symptom management.

Hyperbaric oxygen (HBO_2) consists of exposing individuals to pressures greater than sea level (typically 2–3 atmospheres absolute, ATA), with inhalation of > 99% oxygen, and is used to treat acute carbon monoxide (CO) poisoning, decompression sickness, arterial gas embolism, late effects of radiation injury, certain poorly healing wounds, sudden acute hearing loss, necrotizing fasciitis, and other indications. Exposure times range from 1 to several hours, generally once per day[15]. For sequelae after brain injury, 1.5 ATA has been studied[15]. Prior trials of HBO_2 show encouraging results for improvement of sequelae months to years after traumatic brain injury (TBI)[16–18], stroke[19], and long COVID[20,21].

We conducted this prospective, randomized, blinded sham-controlled clinical trial of HBO_2 to determine the effect size and variance of 40 HBO_2 or sham chamber sessions on persistent symptoms months to years after TBI, hypoxia, and CO poisoning. Secondary objectives included the gathering of data about the effect of an additional 40 HBO_2 sessions administered unblinded after a 3-month washout period (6 months after randomization), identification of effective recruitment and retention strategies and utility of secondary outcome measures in the study population. We selected a unique sham protocol to minimize physiological effect, and the study design specified long-term follow-up.

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Methods

Hyperbaric Oxygen for Traumatic and Non-traumatic Brain Injury (HYBOBI2) was a Phase II, exploratory, randomized, double blind, sham-controlled trial of HBO_2 for community-dwelling adults with persistent symptoms due to brain injury (registered at www.clinicaltrials.gov, NCT01986205 on 18/11/2013). The study was approved by the Intermountain Health Institutional Review Board and followed Good Clinical Practice (GCP) guidelines for conduct of clinical trials. The study was conducted at LDS Hospital (Salt Lake City, Utah, USA) and Intermountain Medical Center (Murray, Utah, USA), both owned by Intermountain Health, a not-for-profit healthcare system.

Participants were recruited through IRB-approved flyers distributed to local clinics, outreach to advocacy groups and brain injury clinicians, public health fairs, and media releases. Interested individuals were initially screened by phone. Those who screened favorably were invited to in-person screening following informed consent. Participants were enrolled by research personnel and clinicians who were blind to allocation.

Participants

Participants were 18–70 years old, with brain injury at least 6 months but no more than 10 years before enrollment. Eligible brain injury etiologies included TBI, which was classified as mild, moderate, or severe according to Department of Defense (DoD) criteria[22], CO poisoning[7], and hypoxia[3]. Those with stroke were not enrolled because we lacked access to stroke outcome measures.

Lifetime brain injury history and associated symptoms were solicited via structured clinical interview[23], with follow-up probes specific to brain injury types as needed. Participants' available medical records from the time of injury were reviewed when additional clarity was needed.

At least three of the following persistent symptoms from the qualifying injury were required: headaches, dizziness or balance problems, blurred vision, tiredness/fatigue or sleep problems, seizures, remembering things or solving problems, managing stress or emotional upsets, controlling temper/irritability, depression, anxiety, post-traumatic stress, or tinnitus. If multiple lifetime brain injuries culminated in persistent symptoms, novel onset or definitive worsening of at least three symptoms at the qualifying injury was required. When a participant had multiple brain injuries that met study inclusion criteria, the most recent was recorded as the qualifying brain injury.

When a participant had trouble isolating individual injuries (e.g., during a youth sport), but ≥1 mild TBI (per DoD criteria[22]) occurred, the series was counted as a singular mild TBI. A head impact not meeting TBI criteria but resulting in new or worsening symptoms was considered a symptomatic head deceleration event and counted separately from lifetime brain injuries[24,25].

Additional inclusion criteria included the ability to speak and write English as a primary language (due to English-language assessments), equalize middle ear pressure, and tolerate the chamber environment; clinically normal thyroid confirmed by thyroid stimulating hormone (TSH), with or without therapy; and hematocrit (HCT) value greater than 35%.

Exclusion criteria included conditions that raised the relative risk for adverse events during HBO_2: insulin-dependent diabetes mellitus, uncontrolled seizure disorder, claustrophobia, implanted devices, pregnancy, lung disease, malignancy, and heart or renal failure. We excluded individuals receiving HBO_2 within the past year and those with conditions that could confound outcome assessments: walking instability, dysarthria preventing examiner comprehension, blindness, deafness, substance abuse, degenerative neurological disease, participation in activities with high risk for future brain injury, prior therapeutic radiation to the central nervous system, pre-injury diminished capacity, or any known, untreated psychiatric or medical condition that might confound outcome assessments or inhibit protocol compliance. Participants were stable on therapy before enrollment. Reasons for ineligibility/declining enrollment were documented at screening.

Trial design

(Figure 1). Participants were stratified by injury type (TBI or non-TBI) and randomized (1:1) to receive 40 HBO_2 or sham sessions. The Intermountain Statistical Data Center created the randomization schedule using random numbers. Randomization assignments were sealed in sequentially numbered opaque envelopes opened by chamber operators. During blinded chamber sessions, the console and pressure gauges were obscured from view to all but the chamber operator[26]. The facility where blinded sessions were administered operated four monoplace chambers in an open room, with chambers operating simultaneously for research and clinical operations. Any noise differences between sham and HBO_2 sessions would not have been discernable in this environment. Investigators and evaluators were not located in the hyperbaric chamber area during this phase of the study. Therefore, any opportunity for these staff to learn a participant's allocation was unlikely. No interim analysis was conducted. After study completion, data analysts conducted between and within-group comparisons using a generic allocation code ("Group A" and "Group B"). After analyses were completed, investigators were unblinded.

Interventions

Blinded interventions were completed in monoplace hyperbaric chambers (Sechrist Industries, Anaheim, CA.). Participants completed 40 chamber sessions within 12 weeks. Sessions were individually scheduled Monday-Friday. This study took place at an altitude of 1500 m. The barometric pressure typically is 12.5 psia or 0.85 ATA or 86.15 kPa. Those assigned to the HBO_2 group were compressed in the hyperbaric chamber to 1.5 ATA (152 kPa; 16.9 psig). Once at pressure, the participant breathed > 99% oxygen through a facemask for 10 min to allow the chamber atmosphere to exceed 99% oxygen[27,28], then removed the facemask to breathe the chamber atmosphere for the duration of the session. This was done to make inhaled oxygen concentration and duration

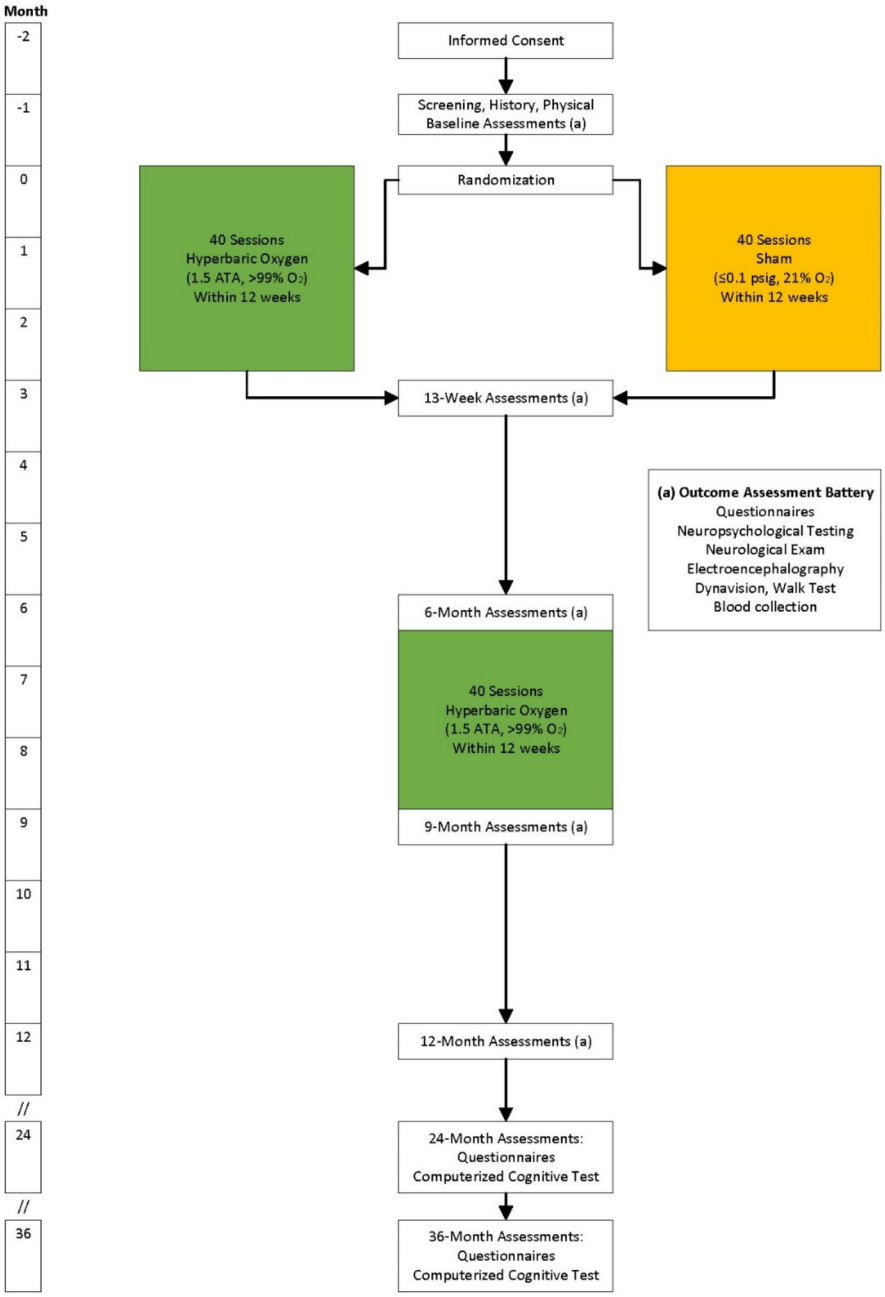

Fig. 1. Study flow diagram.

comparable between the monoplace and multiplace chamber sessions. Time at 1.5 ATA was 50 ± 2 min, and compression/decompression intervals each 5 ± 1 min (60 min door-to-door).

Participants assigned to the sham group followed the same procedure, except room air flowed through the mask and chamber. Chamber pressure did not exceed 0.1 psig over atmospheric pressure (this equals an increase over atmospheric pressure of 0.007 ATA units, or 0.69 kPa), and air flow through the chamber exceeded 70 L/minute. The sham exposure to very minimal chamber pressure has no known therapeutic benefit, but still required middle ear pressure equalization. Allocation concealment is protected using this method[26,29].

Three months later, participants were offered an open HBO_2 intervention of 40 chamber sessions (60 min door-to-door) in a multiplace chamber at 1.5 ATA over 12 weeks. Sessions were offered at a fixed time, Monday-Friday.

Sample characterization and adverse events

At enrollment, participants underwent a brief physical examination by medically licensed, trained personnel, which included visual inspection of tympanic membranes and vital signs measurement. To confirm study eligibility, participants completed a urine drug screen, and women of childbearing potential completed a urine pregnancy test. Participants reported current medications and therapies and full medical history.

During chamber intervention periods, visual acuity was measured weekly, and women of childbearing potential completed a monthly urine pregnancy test. Subsequent vital signs were not routinely checked. Tympanic membranes were inspected only for ear complaints, following procedures that maintained allocation concealment. Chamber operators (unblinded) asked participants about medication updates and adverse events (AEs) at each chamber session. A physician who was blinded to randomization assignment determined the relationship of AEs to study participation (intervention and assessments). AEs were considered protocol-related if the attribution assigned was definite, probable, or possible.

Research personnel (blinded to randomization assignment) also solicited AEs at assessment intervals through 12 months, and updated medical history, new possible head injuries, and serious adverse events at all subsequent assessments. Urine drug screens were repeated through 12 months.

Primary and secondary outcomes

(Table 1). Participants were evaluated before the blinded intervention ("baseline"), after the blinded intervention ("13-weeks"), prior to and following the open intervention ("6-months" and "9-months", respectively), and at 12 months post-randomization ("12-months"). Participants were then assessed annually until study closure ("24-months" and "36-months"). Assessments were completed in-person, though the protocol was amended later to permit remote data collection of some measures due to COVID-19 clinic restrictions or participants moving out-of-area. Assessments were conducted outside standard business hours occasionally to accommodate participant schedules.

The study's a-priori primary outcome was change from baseline in the total Neurobehavioral Symptom Inventory (NSI) score at 13 weeks, like other HBO_2 and TBI trials[16,18]. This self-report measure assesses 22 common symptoms following brain injury[30]. Individuals rate symptom severity over the last 2 weeks on a 5-point Likert scale [0 = None, 4 = Very severe]. The NSI has been validated in studies of traumatic brain injury and hypoxic brain injury[31,32].

Secondary outcomes included the NSI at 6, 9, 12, 24, and 36 months. Because prior trials[16,18,33] suggested PTSD may influence HBO_2 effects, we also analyzed NSI results by PTSD symptom severity.

Additional self-report questionnaires[34–46] and the Automated Neuropsychological Assessment Metrics (ANAM)[47] were administered at all seven assessments intervals. The Patient Global Impression of Change (PGIC)[45] was administered beginning at the 13-week assessments. Assessments through 12 months included a comprehensive battery of neuropsychological tests[48–59] with formal and embedded measures of performance validity[51,60], University of Pennsylvania Smell Identification Test (UPSIT)[61], Dynavision[62], 6 min walk test (6MWT)[63], and a neurological examination. Neurological examination elements included eye movements, near point of convergence[46], auditory by finger rub, upper extremity tremor, finger-to-nose, rapid supination/pronation, pronator drift, Romberg, Sharpened Romberg[64], and tandem gait. Electroencephalography (EEG) was attempted at baseline, 13 weeks, and 6–12 months (Supplementary Methods 1). Blood was drawn for future analyses. The Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II)[57] was administered at baseline to estimate current intellectual ability, and again at 12 months. To evaluate allocation concealment, participants were asked at 13 weeks and 9 months whether they thought they received HBO_2 or regular air for their blinded intervention. A structured exit interview was conducted at the conclusion of the 12-month assessments. The administration order for questionnaires and neuropsychological tests was standardized, and testing was completed over 2–3 days to minimize participant fatigue.

Statistical analysis

The intended sample size was 75 participants in each group, from which we estimated a confidence interval width of 10.2 for total NSI score. We tested baseline and change from baseline differences between and within interventions using paired t-tests for within-group analyses and independent t-tests for between-group analyses. When the assumption of equal error variances was violated at baseline or 13 weeks, Wilcoxon's signed rank tests and Mann-Whitney U tests were used for within and between-group analyses, respectively. Categorical data were analyzed with Pearson's chi-square test[65,66] unless a cell size was less than five participants, for which Fisher's exact test was used. A chi-square goodness of fit test was also used for categorical data with no statistically significant between-group differences. We conducted multiple linear regression to look at the effect of post-randomization brain injuries on the NSI change score from baseline to 12 months. Intention-to-treat results for the primary and secondary outcomes are presented. A per-protocol analysis was also performed on the prime outcome to estimate the effect of protocol adherence. A value of $p < 0.05$ was considered significant.

In this report, "HBO_2 group" refers to participants who were randomized to receive HBO_2 during the 40 blinded sessions (first chamber series), while the "sham group" refers to participants randomized to receive sham chamber sessions during the 40 blinded sessions. All participants were offered 40 HBO_2 sessions during the later open-label series.

Assessment	Description	Administration					
		Baseline	13 wk.	6 mo.	9 mo.	12 mo.	Annual
Neurobehavioral Symptoms Inventory (NSI)[a]	Severity of 22 symptoms over last 2 weeks, 5-point Likert rating[30]	S	S	S	S	S	S
Rivermead Post-Concussion Symptoms Questionnaire (RPQ)[a]	Severity of 16 symptoms in prior 24 h compared to before injury[34]	S	S	S	S	S	S
World Health Organization Quality of Life (WHOQOL-BREF)[a]	26 items covering physical, psychological, emotional, and social health[35]	S	S	S	S	S	S
Centers for Epidemiological Studies – Depression Scale (CES-D)[a]	Frequency of 20 depression symptoms over the past week[36]	S	S	S	S	S	S
Beck Anxiety Inventory (BAI)[a]	Severity of 21 somatic/cognitive anxiety symptoms over the past week[37]	S	S	S	S	S	S
Mayo-Portland Adaptability Inventory-4 (MPAI)[a]	Physical, thinking, mood, and social difficulty interference with daily life[38]	S	S	S	S	S	S
Post-Traumatic Stress Disorder Checklist – Civilian Version (PCL- C)[a]	Severity of 17 PTSD symptoms over the past month, based on the Diagnostic and Statistical Manual of Mental Disorders-IV-TR[39]	S	S	S	S	S	S
Headache Impact Test (HIT-6)[a]	Intensity and impact of headaches over the past 4 weeks[40]	S	S	S	S	S	S
STOP-Bang Questionnaire[a]	Sleep apnea risk factors (snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference, and gender) [41]	S	S	S	S	S	S
Pittsburgh Sleep Quality Index (PSQI)[a]	Sleep quality and quantity, medication, daytime dysfunction in past month[42]	S	S	S	S	S	S
Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)[a]	Screening too for alcohol use affecting health and safety[43]	S	S	S	S	S	S
Glasgow Outcome Scale-Extended (GOS-E)[a]	Recovery after brain injury ranging from death to good recovery[44]	E/S	E/S	E/S	E/S	E/S	E/S
Patient Global Impression of Change (PGIC)[a]	1 question on patient perception of overall improvement compared to baseline[45]		S	S	S	S	S
Allocation Questionnaire[a]	Participant selected whether they believed they received HBO_2, regular air, or "not sure" during the blinded chamber series		S		S		
Vestibular Symptoms Questionnaire (VSQ)[a]	Structured interview on vestibular symptom severity, and triggers[46]	E	E	E	E	E	E
Exit Interview[a]	Structured, open-ended questions asking about study experience					E	+
California Verbal Learning Test-II (CVLT-II)[b]	Learning and memory for verbally presented items, alternate form at 13 weeks and 9 months[48]	E	E	E	E	E	
Brief Visuospatial Memory Test-Revised (BVMT-R)[c]	Learning and memory for visually presented designs, different form presented at each interval[49]	E	E	E	E	E	
Wechsler Adult Intelligence Scale-IV Digit Span[c]	Attention, working memory. Mentally maintain and manipulate a set of numbers[50]	E	E	E	E	E	
WAIS-IV Symbol Search and Coding subtests[c]	Processing speed. Timed test of visual search and match and timed test of identifying and copying symbols associated with numbers[50]	E	E	E	E	E	
Test of Memory Malingering (TOMM)	Forced-choice performance validity test, recognition of visual stimuli[51]	E	E	E	E	E	
Grooved Peg Board[d]	Fine motor speed and dexterity[52]	E	E	E	E	E	
Letter Fluency & Category Fluency[d]	Executive function. Generate words starting with a letter, then in a semantic category. Alternate FAS/Animal and BHR/Clothing at each interval[53,54]	E	E	E	E	E	
Trail-Making Test (TMT) Part A[d]	Processing speed. Basic sequencing task for graphomotor speed[55]	E	E	E	E	E	
TMT Part B[d]	Executive function. Rapid alternating visuomotor sequencing task[55]	E	E	E	E	E	
Stroop Color and Word Test (SCWT)[e]	Word and Color pages (processing speed: word reading, color naming), Color-Word Page (executive function: inhibition of verbal pre-potent response) [56]	E	E	E	E	E	
Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II)[c]	Intellectual ability. Block design (assemble blocks into abstract designs), vocabulary (word knowledge), matrix reasoning (visual abstract reasoning), and similarities (verbal abstract reasoning) subtests[57]	E				E	
Automated Neuropsychological Assessment Metrics (ANAM)[b]	Computerized tests of attention, processing speed, working memory, learning, and memory (normative data-community dwelling adults) [47]	C	C	C	C	C	C
Blood collection	Stored sera, plasma, and DNA for future analysis	P	P	P	P	P	
Neurological Exam[a] by physician or advanced practice clinician	Eye movement, near point of convergence[46], finger rub hearing, tremor, cerebellar function (finger to nose, arm rapid supination/pronation), Romberg (standing, feet together, arms stretched forward), Sharpened Romberg[64] (arms crossed over chest, tandem stance heel to toe, eyes closed, head/neck neutrally positioned, normal = 30 s on any attempt, two attempts for each foot back), tandem gait	E	E	E	E	E	

Continued

Assessment	Description	Administration					
		Baseline	13 wk.	6 mo.	9 mo.	12 mo.	Annual
University of Pennsylvania Smell Identification Test (UPSIT)	40-item test for loss of olfaction. [61] Age/sex normed for normal/abnormal at baseline, raw scores were used for statistical analyses.	E	E	E	E	E	
Dynavision 60 s Self-Paced Trial and 60 s Forced Attention Trial	Visuomotor reaction time to central/peripheral visual stimuli. Tap randomly illuminated lights with and without a competing visual distraction task[62]	C	C	C	C	C	
6 min Walk Test	Walking distance in meters covered in 6 min[63]	E	E	E	E	E	
Electroencephalogram (EEG)	26-lead clinical EEG	E	E	+	E	+	

Table 1. Outcome assessments. *S* self-administered via paper and pencil or computer, with examiner available in person or by telephone address questions from the participant, *E* trained examiner asked questions or administered testing, *P* phlebotomist, *C* trained examiner set up computerized program and delivered general instructions; participants' output recorded by technology. [a]Collected remotely during COVID-19 interruptions or when participant re-located, partial neurological exam completed via video. [b]Normative data based on age, sex[47,58]. [c]Normative data based on age. [d]Normative data based on age, sex, education, race[59]. [e]Normative data based on age, education. +If not administered at the previous assessment.

Results

Patient characteristics and randomization

Participants were recruited from September 10, 2018 to April 28, 2021, when the trial was stopped due to exhausted funding and slowed recruitment. In that interval, 49 participants were randomized (26 to the HBO_2 group, 23 to the sham group) (Fig. 2). After randomization, two sham participants were found ineligible and excluded; the final sample was 47 participants. There were no significant differences between groups in age, education, marital status, employment, race/ethnicity, and body mass index (Table 2). Estimated pre-morbid IQ was average or above for both groups (mean WASI-II Full Scale IQ, HBO_2 111.2 ± 8.6, sham 119.6 ± 20.6). More sham participants used hypnotics or sedatives at baseline compared to the HBO_2 group. Data at the prime outcome interval was analyzed on 42 participants (16 mild TBI, 4 severe TBI, 4 CO in HBO_2; 11 mild TBI, 4 moderate TBI, 1 severe TBI, 1 CO, 1 hypoxic in sham) due to participant withdrawal of 5 participants (2 mild TBI in HBO_2; 1 moderate TBI, 1 severe TBI, 1 CO in sham) prior to the 13-week assessments, and on 41 participants for the prime outcome measure due to 1 HBO_2 participant with a mild TBI not being administered the NSI at the 13 week assessments due to tester error. Most participants (61.7%) suffered a single lifetime brain injury (HBO_2 65.4%, sham 57.1%, $p = 0.56$). Four participants with a mild TBI qualifying injury had suffered a more severe TBI earlier in life (moderate TBI: 1 HBO_2, 1 sham; severe TBI: 1 HBO_2) or another type of brain injury (CO poisoning: 1 HBO_2). Three participants in each group reported symptomatic head deceleration events (1 event: 2 HBO_2, 3 sham; 3 events: 1 HBO_2) in addition to their qualifying and lifetime brain injuries. One participant (HBO_2 group) who had suffered CO poisoning received HBO_2 treatment 1.3 years prior to randomization. Up to 5 other participants may have received prior HBO_2 treatment, all over 6 years prior to randomization.

Study operations were interrupted due to the COVID-19 pandemic, affecting the study timeline of 17 participants (10 HBO_2, 7 sham). Chamber sessions were paused for 9 participants (5 HBO_2, 4 sham), while 5 participants' scheduled chamber start dates were delayed (2 HBO_2, 3 sham). Six participants had delayed outcome assessments (4 HBO_2, 2 sham), and 4 had incomplete outcome assessments (3 HBO_2, 1 sham). After study activities resumed, 3 participants (1 HBO_2, 2 sham) did not continue their blinded chamber sessions. Forty-one participants completed the primary outcome assessment at 13 weeks. Outcome data was available for 41 participants at 6 months, 37 participants at 9 months, and 37 participants at 12 months (Fig. 2).

Prime outcome

At baseline, there were no significant differences in total NSI score between intervention groups. From baseline to 13 weeks, both groups' total NSI scores decreased: HBO_2 mean difference 10.6, 95% CI [6.0, 15.2], $p < 0.001$; sham mean difference 3.6, 95% CI [0.7, 6.5], $p = 0.02$. The HBO_2 group reported a greater reduction in symptoms than the sham group (mean difference 7.0, 95% CI [1.7, 12.3], $p = 0.01$) and had decreased scores on all 3 NSI subdomains (cognitive, affective, and somatic), while only affective domain scores decreased in the sham group (Table 3).

NSI after 13 weeks

From baseline to 6 months, only the HBO_2 group's improvements were maintained, and the HBO_2 group's change score was greater than the sham group's. Mean total NSI scores at 6 months were not significantly different between intervention groups (Table 4).

In the second chamber series, the HBO_2 group experienced further improvements from 6 months to 12 months, but not from 6 months to 9 months (Table 4). The sham group's scores did not change significantly during the second chamber series. From baseline to 12 months, the HBO_2 group's total change score was greater than that of the sham group, with improved scores in all 3 subdomains.

Only 2 eligible participants (1 HBO_2, 1 sham) declined the 24-month assessments (11 HBO_2, 7 sham completed); no eligible participants declined at 36 months (7 HBO_2, 6 sham completed). From baseline to 24 months, only the HBO_2 group's total NSI score significantly improved. Both groups reported a significant decrease in symptoms from baseline to 36 months (Supplementary Table 1).

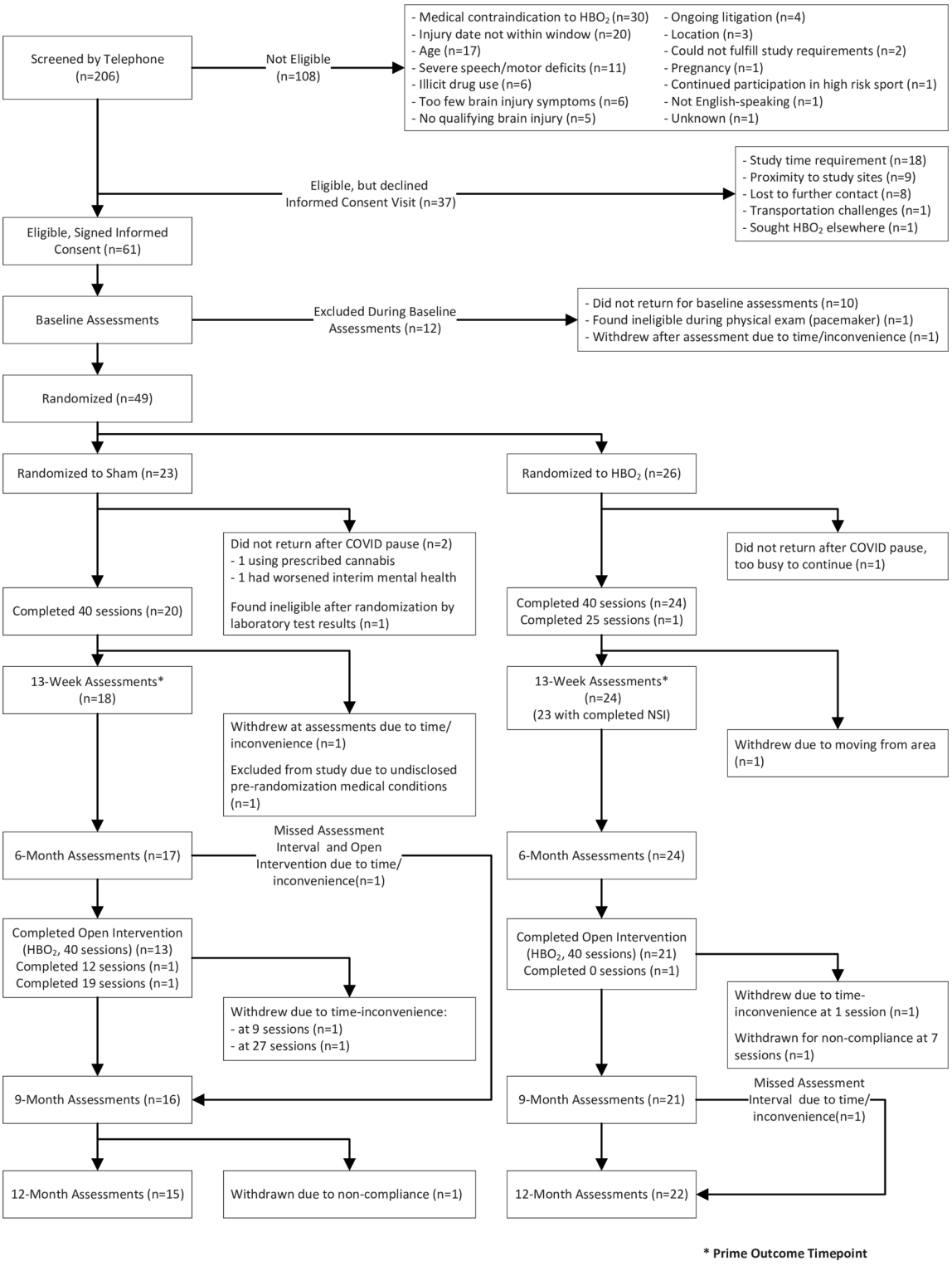

Fig. 2. CONSORT diagram. Individuals screened, enrolled, randomized, and assessed throughout the study.

PTSD subgroup analyses

Individuals were included in the PTSD subgroup if their PCL-C score was ≥ 50 at baseline. Within the HBO_2 group, the PTSD subgroup's NSI change score was greater than that of the non-PTSD subgroup from baseline to 13 weeks (mean difference 12.9, 95% CI [4.5, 21.3], $p = 0.004$), and from baseline to 12 months (mean difference 12.1, 95% CI [1.8, 22.3], $p = 0.02$). There were no significant differences between PTSD vs. non-PTSD HBO_2 subgroups from 6 to 9 months (mean difference 1.7, 95% CI [-13.7, 17.0], $p = 0.82$). Within the sham group, the PTSD subgroup's NSI change score was greater than that of the non-PTSD subgroup from 6 to 9 months (mean

Characteristics	HBO_2 Group ($n=26$)	Sham Group ($n=21$)	p-value odds ratio [95% CI]	Total ($n=47$)
Age, years	46.0 ± 11.8	48.8 ± 13.6	0.47	47.2 ± 12.6
Female sex, *n* (%)	14 (53.8)	7 (33.3)	0.16 *OR* 2.3 [0.7, 7.7]	21 (44.7)
White, *n* (%)	26 (100)	20 (95.2)	0.45 *OR* 3.9 [0.2, 100.2][d]	46 (97.9)
Hispanic or Latino/a, *n* (%)	2 (7.7)	0 (0)	0.50 *OR* 4.4 [0.2, 96.5][e]	2 (4.3)
Left-handed, *n* (%)	1 (3.8)	3 (14.3)	0.31 *OR* 0.2 [0.02, 2.5]	4 (8.5)
Body mass index	28.1 ± 6.3	28.6 ± 7.4	0.79	28.3 ± 6.8
Years of education, *n* (%)	15.1 ± 2.1	15.6 ± 2.4	0.47	15.3 ± 2.2
Single or divorced, *n* (%)	8 (30.8)	5 (23.8)	0.60 *OR* 1.4 [0.4, 5.2]	13 (27.7)
Working, *n* (%)	14 (53.8)	8 (38.1)	0.28 *OR* 0.5 [0.2, 1.7]	22 (46.8)
Qualifying Injury, *n* (%)				
Traumatic brain injury	22 (84.6)	18 (85.7)	1.00	40 (85.1)
Mild	18 (69.2)	11 (52.4)	0.03	29 (61.7)
Moderate	0 (0)	5 (23.8)		5 (10.6)
Severe	4 (15.4)	2 (9.5)		6 (12.8)
Carbon Monoxide Poisoning	4 (15.4)	2 (9.5)	n/a	6 (12.8)
Hypoxia	0 (0)	1 (4.8)		1 (2.1)
Time from qualifying brain injury, years	4.0 ± 2.5	4.3 ± 2.7	0.74	4.2 ± 2.5
Lifetime brain injuries, number of occurrences per participant	1.7 ± 1.3	1.9 ± 1.2	0.65	1.8 ± 1.2
BAI Low (or no) anxiety, *n* (%)	23 (92.0)	17 (81.0)	0.39 *OR* 2.7 [0.4, 16.5]	40 (87.0)
CES-D No to mild depressive symptomatology, *n* (%)	7 (26.9)	7 (33.3)	0.63 *OR* 0.7 [0.2, 2.6]	14 (29.8)
AUDIT-C Below cut-off, *n* (%)	21 (80.8)	20 (95.2)	0.20 *OR* 0.2 [0.02, 2.0]	41 (87.2)
PCL-C Below cut-off, *n* (%)	19 (73.1)	14 (66.7)	0.63 *OR* 1.4, [0.4, 4.8]	33 (70.2)
UPSIT Normal, *n* (%)	15 (57.7)	13 (61.9)	0.77 *OR* 0.8 [0.3, 2.7]	28 (59.6)
Medications: *n* (%) using ≥ 1[b]				
Total number of medications used	3.4 ± 2.5	4.9 ± 3.5	$p=0.10$	4.0 ± 3.1
Antidepressants & anti-anxiety, *n* (%)	9 (34.6)	11 (52.4)	$p=0.22$	20 (42.6)
Stimulants, *n* (%)	7 (26.9)	6 (28.6)	$p=0.9$	13 (27.7)
Hypnotics & sedatives, *n* (%)	7 (26.9)	13 (61.9)	$p=0.02$	20 (42.6)
Headache medications, *n* (%)	5 (19.2)	6 (28.6)	$p=0.51$	11 (23.4)
Narcotic pain control, *n* (%)	3 (11.5)	4 (19.0)	$p=0.7$	7 (14.9)
Non-narcotic pain control, *n* (%)	9 (34.6)	7 (33.3)	$p=0.93$	16 (34.0)
Sleep-specific (excluding hypnotics & sedatives), *n* (%)	2 (7.7)	2 (9.5)	$p=1.0$	4 (8.5)
Other medications, *n* (%)	18 (69.2)	17 (81.0)	$p=0.51$	35 (74.5)
Vitamins and Supplements: *n* (%) using ≥ 1				
Melatonin, *n* (%)	7 (26.9)	2 (9.5)	$p=0.16$	9 (19.1)
Other vitamins & supplements, *n* (%)	16 (61.5)	14 (66.7)	$p=0.72$	30 (63.8)
Therapy usage: *n* (%) using ≥ 1				
Psychotherapy/ Counseling, *n* (%)	8 (30.8)	6 (28.6)	$p=0.87$	14 (29.8)
Cognitive rehabilitation or speech therapy *n* (%)	4 (15.4)	7 (33.3)	$p=0.18$	11 (23.4)
Occupational or vision therapy, *n* (%)	5 (19.2)	3 (14.3)	$p=0.72$	8 (17.0)
Physical therapy, *n* (%)	1 (3.8)	3 (14.3)	$p=0.31$	4 (8.5)
Sleep apnea therapy (CPAP, BIPAP), *n* (%)	0 (0)	1 (4.8)	$p=0.45$	1 (2.1)
Other therapy, *n* (%)[c]	10 (38.5)	4 (19.0)	$p=0.21$	14 (29.8)

Table 2. Participant baseline characteristics[a]. *TBI* traumatic brain injury, *AUDIT-C* Aalcohol use disorders identification test-concise, *PCL-C* PTSD checklist-Ccivilian version, *UPSIT* University of Pennsylvania smell identification test, *CES-D* Center for Epidemiologic Studies-Depression Scale, *BAI* Beck Anxiety Inventory. [a]Plus-minus values are means ± 1 standard deviation. [b]Medications are classified according to the type of condition treated. [c]Acupuncture, aromatherapy, chiropractic care, dry needling, ear plugs or headphones (specialty fit or designed), massage therapy, structural integration therapy. [d]Odds ratio computed with Haldane-Anscombe[65,66] correction because the HBO_2 group is zero. [e]Odds ratio computed with Haldane-Anscombe[65,66] correction.

	Baseline			13 weeks				6 months				12 months			
	n	Mean (SD)	*p*-value	*n*	Mean within-group difference from baseline [95% CI]	*p*-value	Mean between-group difference from baseline [95% CI]	*p*-value	*n*	Mean within-group difference from baseline [95% CI]	*p*-value	Mean between-group difference from baseline [95% CI]	*p*-value	*n*	Mean within-group difference from baseline [95% CI]	*p*-value	Mean between-group difference from baseline [95% CI]	*p*-value
NSI Total																		
HBO_2	26	35.9 (15.8)	0.28	23	10.6 [6.0, 15.2]	<0.001	7.0 [1.7, 12.3]	0.01	24	9.5 [6.0, 13.0]	<0.001	6.4 [1.3, 11.6]	0.02	22	14.9 [10.1, 19.6]	<0.001	10.7 [4.0, 17.5]	0.003
Sham	21	30.7 (16.9)		18	3.6 [0.7, 6.5]	0.02			17	3.1 [-0.9, 7.0]	0.12			15	4.1 [-0.6, 8.8]	0.08		
NSI Cognitive																		
HBO_2	26	9.3 (3.4)	0.15	23	2.5 [0.9, 4.1]	0.003	1.7 [-0.2, 3.7]	0.06	24	2.3 [1.0, 3.5]	0.001	1.5 [-0.3, 3.3]	0.11	22	3.7 [2.2, 5.3]	<0.001	3.0 [0.9, 5.1]	0.006
Sham	21	7.8 (4.0)		18	0.8 [-0.2, 1.7]	0.10			17	0.8 [-0.6, 2.1]	0.24			15	0.7 [-0.5, 2.0]	0.24		
NSI Affective																		
HBO_2	26	13.3 (5.9)	0.44	23	4.2 [2.7, 5.8]	<0.001	2.5 [0.3, 4.7]	0.03	24	3.8 [2.3, 5.4]	<0.001	2.1 [-0.2, 4.3]	0.07	22	6.4 [4.6, 8.2]	<0.001	4.8 [2.3, 7.3]	<0.001
Sham	21	11.9 (7.2)		18	1.7 [0.1, 3.3]	0.04			17	1.8 [0.1, 3.4]	0.04			15	1.6 [-0.1, 3.3]	0.06		
NSI Somatic																		
HBO_2	26	13.2 (8.2)	0.36	23	3.9 [1.6, 6.2]	0.002	2.8 [-0.1, 5.6]	0.06	24	3.4 [1.5, 5.3]	0.001	2.9 [0.1, 5.7]	0.04	22	4.7 [2.4, 7.1]	<0.001	2.9 [-1.0, 6.8]	0.14
Sham	21	11.0 (8.1)		18	1.1 [-0.4, 2.7]	0.15			17	0.5 [-1.6, 2.6]	0.60			15	1.8 [-1.7, 5.3]	0.29		

Table 3. Neurobehavioral Symptom Inventory (NSI). Baseline scores (mean and standard deviation), mean within-group difference from baseline at each outcome period (baseline score – follow-up score), and mean between-group difference from baseline at each outcome period (HBO_2 – sham). Lower baseline scores are favorable, positive within-group change scores indicate improvement, and positive between-group mean differences favor the HBO_2 group.

	6 months			9 months					12 months				
	n	Mean (SD)	*p*-value	*n*	Mean within-group difference from 6 months [95% CI]	*p*-value	Mean between-group difference from 6 months [95% CI]	*p*-value	*n*	Mean within-group difference from 6 months [95% CI]	*p*-value	Mean between-group difference from 6 months [95% CI]	*p*-value
NSI Total													
HBO_2	24	25.9 (15.0)	0.80	21	0.6 [-4.4, 5.7]	0.80	-1.7 [-8.2, 4.8]	0.59	22	6.6 [2.2, 10.9]	0.005	4.0 [-2.5, 10.6]	0.22
Sham	17	27.2 (17.2)		15	2.3 [-1.0, 5.7]	0.16			14	2.5 [-2.5, 7.6]	0.29		
NSI Cognitive													
HBO_2	24	7.2 (4.3)	0.94	21	0.7 [-0.8, 2.2]	0.34	0.2 [-1.9, 2.2]	0.86	22	1.4 [0.1, 2.6]	0.03	0.9 [-1.0, 2.7]	0.36
Sham	17	7.1 (3.8)		15	0.5 [-0.7, 1.8]	0.38			14	0.5 [-1.0, 2.0]	0.48		
NSI Affective													
HBO_2	24	9.3 (5.6)	0.83	21	0.1 [-1.9, 2.1]	0.92	-0.4 [-2.6, 1.8]	0.73	22	3.0 [1.3, 4.6]	0.001	2.8 [0.3, 5.3]	0.03
Sham	17	9.8 (7.1)		15	0.5 [-0.5, 1.4]	0.31			14	0.1 [-1.8, 2.1]	0.88		
NSI Somatic													
HBO_2	24	9.4 (7.2)	0.68	21	-0.2 [-2.6, 2.2]	0.87	-1.5 [-4.7, 1.7]	0.34	22	2.3 [0.4, 4.2]	0.02	0.3 [-2.8, 3.5]	0.83
Sham	17	10.4 (7.8)		15	1.3 [-0.6, 3.3]	0.17			14	1.9 [-0.9, 4.7]	0.16		

Table 4. 6-month Neurobehavioral Symptom Inventory (NSI). Six- month assessment scores (mean and standard deviation), mean within-group difference from 6 months at each outcome period (baseline score – follow-up score), and mean between-group difference from 6 months at each outcome period (HBO_2 – sham). Lower baseline scores are favorable, positive within-group change scores indicate improvement, and positive between-group mean differences favor the HBO_2 group.

difference 9.7, 95% CI [5.0, 14.4], $p < 0.001$), but not at other time points (baseline to 13 weeks mean difference 3.0, 95% CI [−3.6, 9.6], $p = 0.34$; baseline to 12 months mean difference − 4.6, 95% CI [−15.4, 6.1], $p = 0.37$).

Secondary outcomes

Full results are shown in Supplementary Tables 2–11. At baseline, the sham group performed better than the HBO_2 group on both the short delay and long delay subtests of the California Verbal Learning Test (CVLT-II), but not on immediate recall nor on percentage of words retained (short delay free recall v Trial 5 z-score mean difference = 0.4, 95% CI [−0.1, 0.9], $p = 0.09$). On the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), 5 HBO_2 participants reported potentially problematic alcohol use, compared to 1 sham participant, but that difference did not reach statistical significance. At 6 months, the sham group performed better than the HBO_2 group on the code substitution delayed subtest of the ANAM, but there were no significant differences on the code substitution learning subtest of the ANAM, in which participants are asked to initially encode information. The HBO_2 group had higher accuracy on the UPSIT compared to sham according to raw score, but not the normed percentile ($p = 0.07$). Otherwise, there were no significant differences between the groups at baseline and 6 months.

Self-report questionnaires other than the NSI

The PGIC was analyzed as a continuous variable as a research measure. At 13 weeks, PGIC scores did not differ significantly between groups, and PGIC scores increased (improved) in both groups between 13 weeks and 12 months. From 6 to 9 months, the sham group reported significantly greater improvement than the HBO_2 group. At 12 months, the mean PGIC score for the HBO_2 group exceeded 5, the threshold for significant, favorable change in a clinical setting.

Only 13% of participants reported moderate or severe anxiety symptoms on the Beck Anxiety Inventory (BAI) at baseline. At 13 weeks, only the HBO_2 group's BAI scores significantly improved (mean difference 3.0, 95% CI [0.7, 5.2], $p = 0.01$). From 6 to 9 months, neither intervention groups' scores changed significantly. The HBO_2 group reported a greater improvement in BAI scores compared to the sham group from baseline to 12 months (mean difference 4.5, 95% CI [0.6, 8.4], $p = 0.03$).

At baseline, 25.5% of participants' Centers for Epidemiological Studies-Depression Scale (CES-D) scores suggested moderate depression and 44.7% suggested severe depression. From baseline to 13 weeks, both groups' CES-D scores improved. This improvement remained significant within the HBO_2 group at 6 months, but not in the sham group. From 6 to 9 months, neither intervention groups' scores changed significantly, and from baseline to 12 months, both groups' scores improved.

From baseline to 13 weeks, both groups' Post-Traumatic Stress Disorder Checklist-Civilian Version (PCL-C) scores improved. Neither intervention groups' scores changed significantly from 6 to 9 months. From baseline to 12 months, only the HBO_2 group's improvement was significant.

Both groups' headache impact test (HIT-6) scores improved from baseline to 13 weeks, and from baseline to 12 months. There was no difference by intervention. Neither group's scores significantly changed from 6 to 9 months. Only the HBO_2 group's Pittsburgh Sleep Quality Index (PSQI) scores improved from baseline to 13 weeks, and from baseline to 12 months. Neither group's scores significantly changed from 6 to 9 months. On the vestibular symptom questionnaire (VSQ), the number of items endorsed as abnormal decreased in the HBO_2 group from baseline to 13 weeks. Changes at other time points did not reach statistical significance.

On the Glasgow Outcome Scale (GOS-E), the sham group's scores improved from 6 to 9 months. Changes at other time points did not reach statistical significance. From baseline to 13 weeks, both groups' total Mayo-Portland Adaptability Inventory (MPAI-4) scores improved. Both groups' improvements were maintained through 12 months, with the HBO_2 group's change score from baseline to 12 months greater than sham. Neither group's scores significantly changed from 6 to 9 months.

From baseline to 13 weeks, both groups' Rivermead Post-Concussion Questionnaire (RPQ) scores improved. From 6 to 9 months, only the sham group's score improved significantly. From baseline to 12 months, scores improved in both groups with the HBO_2 group reporting a greater improvement than the sham group.

On the World Health Organization Quality of Life (WHOQOL-BREF), both groups' physical health domain scores improved from baseline to 13 weeks, and from baseline to 12 months. In both the psychological and environmental domains, neither group's scores changed significantly from baseline to 13 weeks; only the HBO_2 group reported significant improvement from baseline to 12 months. In the social domain, neither group's scores significantly changed at any point. From 6 to 9 months, no significant changes occurred in any domain.

Neuropsychological testing

Embedded and stand-alone measures of effort indicated that results of neuropsychological testing were valid estimates of current cognitive functioning. From baseline to 13 weeks, the HBO_2 group improved on 7 measures, while the sham group improved on 4. From 6 to 9 months, only the HBO_2 group improved (2 measures). In addition, immediate recall on CVLT-II improved in the HBO_2 group compared to the sham group from 6 to 9 months. From baseline to 12 months, the HBO_2 group improved on 8 measures, while the sham group improved on 10. On category fluency, performance declined from baseline to 13 weeks in the sham group, and from 6 to 9 months in the HBO_2 group, possibly related to use of alternate forms. On BVMT-R, performance declined from 6 to 9 months in the sham group, but their scores returned to baseline by 12 months.

Computerized neurocognitive testing

Both groups' composite ANAM scores improved from baseline to 13 weeks and from baseline to 12 months. From 6 to 9 months, the HBO_2 group improved on simple reaction time; no changes in the sham group reached significance.

Neurological tests

The baseline neurological examination was abnormal in 93.6% of participants, most commonly the Sharpened Romberg[64] time (Supplementary Tables 8–9). There were no consistent improvements in either intervention group.

On Dynavision, both groups improved on forced choice target hits and reaction time from baseline to 13 weeks. Only the HBO_2 group increased self-paced target hits. From 6 to 9 months, the HBO_2 group improved on self-paced target hits and reaction time. From baseline to 12 months, both the HBO_2 and sham groups improved on forced choice target hits and reaction time, and self-paced target hits. In addition, the HBO_2 group improved on self-paced reaction time.

On a performance-based test of olfaction normed for age and gender, the majority of participants' scores were normal at baseline (HBO_2 = 57.7%, sham = 61.9%, $p = 0.77$). Only the HBO_2 group demonstrated significant improvement from baseline to 13 weeks. By 12 months, average accuracy regressed to baseline performance. The sham group significantly declined from baseline to 6 months, but their scores returned back to baseline by 12 months.

Changes in distance walked on the 6MWT test did not reach significance across any time point comparisons for both groups. Both the neurological examination and 6-Minute Walk Test were insensitive to measuring change in this study.

Of 49 baseline EEGs, 10 were abnormal (6 HBO_2, 4 sham). Of 5 participants in the HBO_2 group with a baseline EEG and at least 1 subsequent EEG, 1 participant improved by 13 weeks, 1 by 6 months, and 1 by 9 months. In the sham group at 13 weeks or 6 months, 2 participants improved and 2 were unchanged from baseline. Of 3 participants in the sham group who had an abnormal baseline EEG and a post-HBO_2 EEG, 1 improved and 2 were normal at 9–12 months. Across all participants who received HBO_2 either initially or after 6 months, 6 of 8 improved or normalized. (Supplementary Table 12).

Blinding

Blinding of group allocation was successful at 13 weeks. Following the blinded intervention (at the 13-week assessment), 34.8% ($n = 8$) of participants in the HBO_2 group and 23.5% ($n = 4$) in the sham group correctly guessed their group assignment, while 65.2% ($n = 15$) in HBO_2 and 76.5% ($n = 13$) in sham guessed incorrectly or responded "not sure." Two participants (1 HBO_2, 1 sham) did not receive the questionnaire due to tester error. There was no significant difference in the odds of guessing randomization assignment correctly between groups ($p = 0.55$, *OR* 1.7, 95% CI [0.4, 7.1]), but participants were more likely to guess their randomization assignment incorrectly or respond "not sure" than to guess correctly ($p = 0.01$). At 9 months, after all participants had received HBO_2, more participants correctly selected their original allocation, but were not more likely to select correctly than chance ($p = 0.33$). There were no between-group differences in accuracy (correct: 50% ($n = 11$) HBO_2, 68.8% ($n = 11$) sham; incorrect or "not sure": 50% ($n = 11$) HBO_2, 31.3% ($n = 5$) sham, $p = 0.24$, *OR* 0.4, 95% CI [0.1, 1.8]).

Adverse events

From baseline through the 12-month assessment, chamber-related adverse events were reported by 19 of the 49 participants who were randomized (39%) (Supplementary Table 13). Three participants had adverse events

related to study procedures other than the chamber sessions: a bruise after bumping into study equipment ($n=1$), breach of confidentiality ($n=1$), and syncopal episode during blood draw ($n=1$). No serious adverse events were reported in this time frame. One participant with a pre-existing history of a mood disorder was discontinued in the multiplace sessions after reporting a worsening of symptoms during both the sham and intervention sessions, and subsequently withdrew from the study due to time/ inconvenience. One participant elected to discontinue chamber sessions due to concern of contracting SARS-CoV-2 in the clinic environment and confidentiality concerns but remained enrolled in the study.

During study participation, 5 participants (2 HBO_2, 3 sham) reported one additional mild TBI. One additional HBO_2 participant reported 2 mild TBIs. The injuries were reported at the 13-week (1 HBO_2, 1 sham), 6-month (1 HBO_2), 9-month (1 sham), 12-month (2 HBO_2), and 36-month (1 sham) assessments. Two sham group participants reported a symptomatic head deceleration event not meeting mild TBI criteria (1 at 12 and 24 months, 1 at 36 months), and 1 HBO_2 group participant reported such an event at the 6-month assessment, followed by negative health effects from environmental toxins at the 9-month assessment. Four participants reported unresolved sequelae of a COVID-19 infection[67] at the 9-month (1 HBO_2, increased dizziness and microsmia), 12-month (1 HBO_2, cardiovascular and autonomic abnormalities, myalgia, and cognitive difficulties) and 36-month assessments (2 sham, microsmia, arthralgias/myalgias, fatigue, headaches, dizziness and nausea, and cognitive difficulties). When controlling for randomization group, experiencing additional brain injuries through the 12-month assessments did not influence patient-reported change score on the NSI from baseline to 12 months (estimate − 1.7, 95% CI [-10.3, 6.9], $p=0.69$).

Protocol adherence

Participants who did not complete all 80 chamber sessions fell into two categories: Those who withdrew altogether (4 HBO_2, 15%; 5 sham, 24%) and those who remained enrolled in the study but did not complete all chamber sessions (1 HBO_2, 4%; 3 sham, 14%) (Fig. 2). All HBO_2 group participants who did not complete all 80 chamber sessions had a mild TBI as their qualifying injury and were employed at baseline. In comparison, sham group participants who did not complete all 80 chamber sessions had a more severe qualifying TBI (3 moderate, 2 severe) or CO poisoning (1) and half (4) were on disability.

Per-protocol analysis

See Supplementary Tables 14–15. The only difference between the intention-to-treat analyses and the per-protocol analyses were within the baseline to 9-month assessments. In the intention-to-treat analysis for this interval, the mean difference in the HBO_2 group was 8.4 (95% CI [4.5, 12.2], $p<0.001$) and in the sham group was 4.2 (95% CI [0.6, 7.8], $p=0.02$). The between-group mean difference at this timepoint was 4.2 (95% CI [-1.0, 9.4], $p=0.11$). In the per-protocol analysis for this interval, the mean change score in the sham group was not statistically significant.

Qualitative results

Of 37 participants who completed the exit interview at 12 months, 34 (91.9%) participants endorsed ≥ 1 benefit from study participation, and 3 participants (all HBO_2) did not. The most frequently cited benefits were improvements to overall quality of life (72.7% HBO_2, 53.3% sham), cognition (54.5% HBO_2, 60% sham), and mood (45.5% HBO_2, 40% sham) (Supplementary Table 16).

Discussion

After the blinded, sham-controlled portion of this trial (13 weeks after randomization), both the HBO_2 and sham groups reported improvements in brain injury symptoms compared to baseline (within-group analysis), but participants who received 40 HBO_2 sessions reported greater improvement in brain injury symptoms compared to participants who received 40 sham chamber sessions (between-group analysis). The HBO_2 group also improved on measures of olfaction, anxiety, sleep difficulties, and vestibular complaints. Both groups reported improvements in depression, headaches, PTSD symptoms, physical quality of life, and degree to which difficulties interfere with daily life.

Improvements in symptoms and function may be due to both HBO_2 effects and study participation effects (e.g., expectation of improvement, respite time in the chamber, social interactions, or adding structure or activity to their day). Indeed, during the qualitative exit interviews, participants reported they enjoyed many aspects of the chamber sessions and attributed symptom improvement to participation. Research supports the benefits of downtime, quiet, socialization, and structure for brain injury[68–74]. However, because the degree of improvement on the prime outcome was greater in the HBO_2 group, we conclude that HBO_2 conferred benefit beyond the participation effects that were experienced in both study arms.

Furthermore, unlike the HBO_2 group, benefits in the sham group after the blinded portion of the trial were not maintained 3 months later for most measures. Therefore, improvements from study participation alone appear to wane with time.

Both groups showed improvement on computerized and paper-and-pencil neuropsychological tests of cognitive functioning. Participants completed the same or alternate test versions up to 5 times, and practice effects are expected[75]. While there is some individual susceptibility to practice effects[76,77], all participants received the same battery at similar intervals. Thus, opportunity for improved performance due to repeated testing was equal across groups. The HBO_2 group showed improvement on more individual tests following 40 chamber sessions compared to the sham group, which supports benefit to the HBO_2 group beyond practice effects alone (i.e., improved brain function).

Three months after completion of the blinded sham-controlled portion, all study participants were offered 40 open-label HBO_2 sessions in a multiplace chamber. Therefore, the original sham group received up to 40 HBO_2

sessions and the original HBO_2 group received up to 80 HBO_2 sessions. Following the additional 40 HBO_2 open-label sessions, the participants who received 80 HBO_2 sessions reported greater improvement in total NSI score compared the sham group, who received only 40 HBO_2 sessions, as well as compared to their own total NSI scores after only 40 HBO_2 sessions (Table 4).

After the sham group received these later 40 HBO_2 sessions, their self-reported improvement on the PGIC were statistically significant. These improvements were maintained at follow-up testing 3 months later (12 months post-randomization).

20% of the baseline EEGs were abnormal. In participants with chronic, stable brain injury, serial EEGs done years following brain injury (as in our cohort) across 12 months likely should not change appreciably. In our study, 6 of 8 participants with abnormal EEGs at baseline improved or were normal after receiving HBO_2. Although the sample size is small, this observation of improvement in the EEG after HBO_2 independently supports improvement in brain injury. Many intended EEGs were not done due to inconvenience, study drop-out, and the COVID-19 pandemic.

Results in context

This trial has results consistent with some prospective studies of patients with persistent sequalae after mild TBI, which showed improvement with HBO_2[17,18,33,78,79]. Most prior sham-controlled studies of HBO_2 for the long-term effects of brain injury have focused on military populations[16,18,33,79] which have different demographic considerations (e.g., age, gender, number of TBIs, and presence of blast injury) and comorbid conditions such as high rates of PTSD. This study focused on brain injuries outside of military experience, and the study population included a greater number of females, lower rates of PTSD, and greater heterogeneity of brain injury etiology and age. Therefore, the findings of this study may be more generalizable to community-dwelling adults with brain injury.

The prime outcome, NSI change score after the initial 40 chamber exposures, was much greater in the HBO_2 group in this study (decrease of 10.6 points) compared to two previous studies[16,18] (decrease of 3.6 and 1.2 points, respectively).

This study also offers information on durability of effects after HBO_2 to one year and beyond and suggests that improvements in brain injury symptoms are sustained long-term. One study in a military population[18] had visits at 6 months with telephone visits at one year. Telephone follow-up in a second military study was incomplete[33].

Other recent HBO_2-brain injury randomized clinical trials registered on clinicaltrials.gov include one that is ongoing[80] and 3 that are completed[81–84] (TBI-related fibromylagia[81], PTSD caused by TBI[82,83], and TBI in children[84]). The completed trials all showed benefit with HBO_2. An additional randomized trial demonstrated clinical and brain imaging improvement with HBO_2 in post-COVID-19 condition[20,21,85].

Study strengths and limitations

This clinical trial design is a departure from a traditional sham-controlled intervention trial in that it included a blinded, randomized intervention followed by an open-label intervention. We selected this design to allow comparison of 40 HBO_2 sessions to 40 sham sessions at 13-weeks after randomization, and also compare the effect of 40 HBO_2 sessions to 80 HBO_2 sessions. At the time of our study initiation, other investigations used 40 daily HBO_2 sessions[16–18,86]. In our prior study[28] 60 daily HBO_2 sessions were offered.

Other strengths of this study include that it is a prospective, sham-controlled, double-blind (participants, assessors, data analysts, and investigators) design. This study included comprehensive, clinically important outcomes, face-to-face evaluations by trained and skilled evaluators, and long-term follow-up (including, uniquely, follow up beyond 12 months after randomization). This study used the NSI as the primary outcome measure, which is validated and reliable[31] and was developed to address gaps in other self-report questionnaires following brain injury. Baseline NSI scores in this study were consistent with the brain injury population, and the degree of change suggests that improvements were clinically meaningful. In addition, the NSI captured degree of change in symptoms by intervention that other questionnaires[34] did not. Some prior clinical trials of HBO_2 for brain injury incorporated neuroimaging outcomes[17,18,20], though we elected to forego neuroimaging because of cost, inconvenience, potential risk, and insensitivity[18,87].

At 13 weeks, the blinding of allocation was preserved. At 9 months, after all participants had received HBO_2 and could compare that experience to their first chamber series, a greater number of participants correctly selected their original allocation, as expected.

Participants liked flexibility for scheduling chamber sessions. Occasional assessments outside of standard business hours, as well as use of remote data collection to obtain a subset of the planned battery prevented data loss. Future trials should consider participant scheduling flexibility and remote data collection to improve participant retention and data collection.

This study used intention-to-treat analyses. It is possible that incomplete subject participation influenced outcome; however, a per-protocol analysis of 13-week and 12-month data showed results consistent with the intention-to-treat analyses.

The sham group's total NSI change score did not meet statistical significance between 6 months and 9 months (after they received HBO_2). This contrasts with the HBO_2 group, who improved when they received the initial HBO_2 series. However, the sham group's mean change score was favorable, and when inspecting individual change scores (Fig. 3), most sham participants had improvement after they received HBO_2 during the second chamber series. Improvement was large in a few participants. Comparing the 9-month total NSI change score from baseline in this group did result in statistically significant improvement (mean change 4.2, 95% CI [0.6, 7.8], $p = 0.02$). This suggests benefit from both HBO_2 and study participation activities that only met statistical significance when both factors were combined. That the changes in the sham group from 6 to 9 months (after

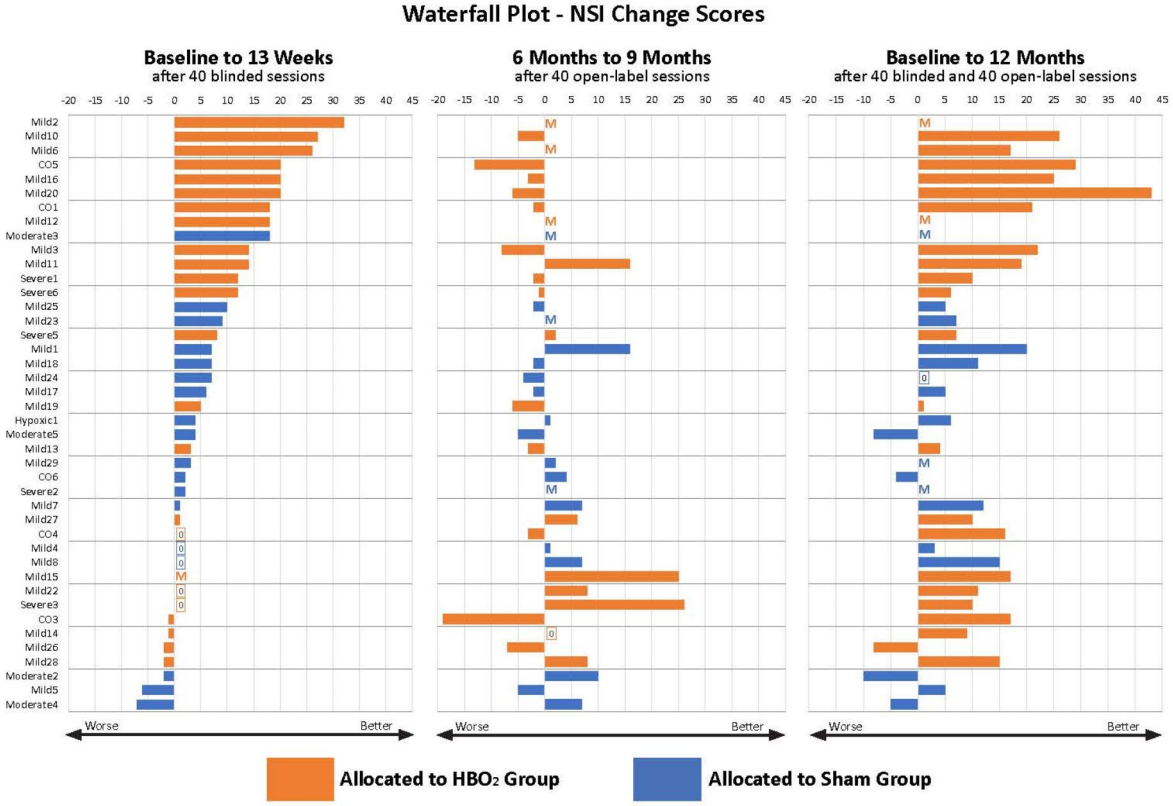

Fig. 3. Waterfall plot of participant total Neurobehavioral Symptom Inventory (NSI) change scores. Participants are sorted by greatest improvement at 13 weeks, by allocation assignment. A 0 indicates no difference between assessment intervals, while an M indicates that the score is missing for at least one assessment point. Participants with IDs of Moderate1, Severe4, CO2 (sham); Mild9 and Mild21 (HBO_2) withdrew before the 13-week assessment.

HBO_2) did not meet statistical significance may also be a result of small sample size (only 13 sham participants received their 40 HBO_2 sessions). This small number in this cohort is most likely due to study participants having challenges meeting the fixed time that the multiplace hyperbaric chamber was available. In addition, the changes in the sham group were not sustained at 12 months which invites further inquiry into dosing, but also may be an artifact of small sample size.

The number of individuals who randomized is approximately one third of our intended sample size. At the prime outcome of 13 weeks, our study results support that a sufficient number of participants enrolled. Nevertheless, the remainder of the study may have been underpowered, which likely influenced the magnitude of effect on outcomes administered after the open label HBO_2 intervention. Additionally, we were only able to enroll 7 participants with brain injury other than TBI. Although their symptom changes trended with the TBI participants, the number of non-TBI participants is too small to confidently extrapolate study results to that population.

Although there was no charge for study participation and participants were given a monetary stipend for follow-up testing, several participants withdrew from the study. This study required daily participation during intervention periods, as well as outcome assessment scheduling, mostly during regular working hours. Even though participants were aware of, and agreed to, the requirements of the study, some of them could not satisfy these requirements. This limitation was more pronounced during the open label portion because the chamber time was set at 11:30 AM. The withdrawals during study participation may have resulted in self-selection bias at

follow-up study assessment intervals. Specifically, individuals who perceived benefit in study participation may have been more likely to complete the open-label chamber sessions and subsequent assessments.

Relatedly, study recruitment and enrollment were likely biased because of the participation demands. Whether this bias influenced study results is unknown.

Interruption to study operations due to the COVID-19 pandemic, stress of a global pandemic on participants, as well as introduction of a novel virus that can cause cognitive sequalae also may have influenced results. It is possible that the pandemic introduced enrollment bias in age or health status of participants. It is also possible that the study outcome data was influenced by study intervention interruption; delayed outcome assessments; or stress or health complications that affected participants' mood, cognitive abilities, post-concussive symptoms, and sense of smell.

This study attempted follow-up at 24 and 36 months after randomization. We are unaware of other HBO_2 studies of brain injury that incorporate 36-month outcome. Of 13 participants who were eligible, follow-up at 36 months showed durable reduction in self-reported post-concussion symptoms.

Conclusions

Like other studies of hyperbaric oxygen (HBO_2) for adverse sequalae after brain injury, our double-blind study found that a course of HBO_2 improved clinically meaningful outcomes. Also, our results suggest 80 HBO_2 sessions may be superior to 40 sessions for treatment of long-term brain injury outcomes.

Data availability

The datasets from which the present results were drawn are not openly available due to reasons of sensitivity and are available from the corresponding author on reasonable request.

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Author contributions

LKW and KD conceived the study. LKW, KD, AR designed the study. LKW, RZ, AR provided study supervision. LKW, RZ, KD contributed to patients' recruitment and data acquisition. RZ and KD performed the data analysis. LKW, RZ, KD wrote the first draft of the manuscript and subsequent revisions. All authors have read and approved the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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