Original Investigation

Effects of Hyperbaric Oxygen on Symptoms and Quality of Life Among Service Members With Persistent Postconcussion Symptoms

A Randomized Clinical Trial

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IMPORTANCE Improvement has been anecdotally observed in patients with persistent postconcussion symptoms (PCS) after mild traumatic brain injury following treatment with hyperbaric oxygen (HBO). The effectiveness of HBO as an adjunctive treatment for PCS is unknown to date.

OBJECTIVES To compare the safety of and to estimate the efficacy for symptomatic outcomes from standard PCS care alone, care supplemented with HBO, or a sham procedure.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, sham-controlled clinical trial of 72 military service members with ongoing symptoms at least 4 months after mild traumatic brain injury. Participants were enrolled at military hospitals in Colorado, North Carolina, California, and Georgia between April 26, 2011, and August 24, 2012. Assessments occurred before randomization, at the midpoint, and within 1 month after completing the interventions.

INTERVENTIONS Routine PCS care was provided in specialized clinics. In addition, participants were randomized 1:1:1 to 40 HBO sessions administered at 1.5 atmospheres absolute (ATA), 40 sham sessions consisting of room air at 1.2 ATA, or no supplemental chamber procedures.

MAIN OUTCOMES AND MEASURES The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) served as the primary outcome measure. A change score of at least 2 points on the RPQ-3 subscale (range, 0-12) was defined as clinically significant. Change scores from baseline were calculated for the RPQ-3 and for the total RPQ. Secondary measures included additional patient-reported outcomes and automated neuropsychometric testing.

RESULTS On average, participants had sustained 3 lifetime mild traumatic brain injuries; the most recent occurred 23 months before enrollment. No differences were observed between groups for improvement of at least 2 points on the RPQ-3 subscale (25% in the no intervention group, 52% in the HBO group, and 33% in the sham group; $P = .24$). Compared with the no intervention group (mean change score, 0.5; 95% CI, −4.8 to 5.8; $P = .91$), both groups undergoing supplemental chamber procedures showed improvement in symptoms on the RPQ (mean change score, 5.4; 95% CI, −0.5 to 11.3; $P = .008$ in the HBO group and 7.0; 95% CI, 1.0-12.9; $P = .02$ in the sham group). No difference between the HBO group and the sham group was observed ($P = .70$). Chamber sessions were well tolerated.

CONCLUSIONS AND RELEVANCE Among service members with persistent PCS, HBO showed no benefits over sham compressions. Both intervention groups demonstrated improved outcomes compared with PCS care alone. This finding suggests that the observed improvements were not oxygen mediated but may reflect nonspecific improvements related to placebo effects.

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Invited Commentary

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Although most military service members sustaining mild traumatic brain injury (mTBI) fully recover within 30 days,[1] some report chronic symptoms following deployment-related injury.[2-4] Common postconcussion symptoms (PCS) include headaches, balance problems, sleep disturbance, fatigue, forgetfulness, poor concentration, irritability, and anxiety.[5,6] While symptom presentation is heterogeneous, data suggest that the frequency and severity of symptoms may be more related to concomitant emotional distress or pain than to a specific mechanism or severity of injury.[7-11] Regardless of contributing factors, few established therapies exist for those with persistent PCS.[12]

Based on previous work for other neurological conditions, interest emerged in hyperbaric oxygen (HBO) as a potential treatment for chronic PCS.[13,14] Clinicians observed improvement in mTBI symptoms following 40 HBO sessions at 1.5 atmospheres absolute (ATA) for 60 minutes.[14] Subsequently, Harch et al[15] demonstrated symptomatic and modest cognitive improvement in a case series of 15 service members with PCS using this regimen. These favorable anecdotes prompted the Department of Defense and the Department of Veterans Affairs to develop a clinical research program to evaluate the safety and efficacy of HBO by treating service members with persistent PCS in a series of randomized, sham-controlled trials.[16] We report the symptom and quality-of-life outcomes from the largest and most rigorous of these preliminary clinical trials to date.

Methods

Study Design and Oversight

The study protocol was approved by the institutional review boards at the US Army Medical Research and Materiel Command and the University of Colorado, as well as local institutional reviews. All study volunteers signed written informed consent. The Hyperbaric Oxygen Therapy for Persistent Postconcussive Symptoms After Mild Traumatic Brain Injury (HOPPS) trial was designed as a 3-group, randomized, double-blind, sham-controlled trial to evaluate changes in baseline concussion symptoms after an intervention period of 8 to 10 weeks. The intervention groups included routine PCS care as practiced within the Department of Defense, routine PCS care supplemented with HBO at the dose of 1.5 ATA for 60 minutes administered weekdays for 40 sessions, and routine PCS care supplemented with an otherwise identical 40 sham sessions of room air pressurized to 1.2 ATA. Randomization used a permuted block method of 1:1:1, stratified by site. The study was conducted at 4 military hospitals using multiplace hyperbaric chambers under an investigational new drug application held by the US Army Office of the Surgeon General.[17]

Selection and Description of Participants:

The HOPPS trial participants were at least 18 years old and still serving in the military and were recruited through hospital-based TBI clinics, referrals from unit medical officers, or self-referrals. Interested service members contacted a civilian study hotline to learn about the study and screen for eligibility after verbal informed consent. Medical history, TBI history determined by a structured clinical interview (Ohio State University TBI Identification),[18] and ongoing symptoms were self-reported. All participants required a history of 1 or more lifetime mTBIs with persistent symptoms, with at least 1 mTBI occurring during deployment to Operation Iraqi Freedom or Enduring Freedom and the most recent at least 4 months before randomization. Comorbidities, such as posttraumatic stress disorder (PTSD) or depressive symptoms, were assessed at enrollment and were not exclusionary, but medication use had to be stable for 30 days. Exclusion criteria included lifetime history of moderate to severe TBI, relative or absolute contraindications to HBO, or current drug abuse. Before randomization, each participant experienced brief chamber pressurization to assess for claustrophobia and ability to equalize ear pressure (eMethods 1 in the Supplement lists detailed inclusion and exclusion criteria).

Interventions

Hyperbaric oxygen was administered daily in an air-filled multiplace chamber at 1.5 ATA for 60 minutes. Participants breathed 100% oxygen delivered by a hood designed for that purpose. Details of the procedure and blinding methods are described in eMethods 2 in the Supplement, and only chamber operators knew the chamber treatment allocation. The sham followed identical chamber procedures; however, the chamber was pressurized to 1.2 ATA (a depth previously shown to mask the pressurization process[19]), and participants breathed room air administered through the hoods. Participants completed 40 sessions within a 10-week period that allowed for other medical and job-related commitments. After completion, volunteers were asked via questionnaire to guess their assignment to HBO or air during chamber sessions.

Assessments and Outcome Measures

Validated outcome measures for interventional trials in PCS are not established to date. The primary outcome was change in concussion symptom scores after the intervention using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ), which queries about symptoms during the past 24 hours compared with preinjury health.[20,21] Because no validated change scores exist, we prespecified a cutoff of a 15% improvement that we deemed clinically relevant, translating to a change score of at least 2 points on the RPQ-3 subscale (score range, 0-12). Change scores over time in patient-reported outcomes are anchored individually from the baseline values, and a positive change indicates a favorable response by convention.

Secondary self-reported symptom outcomes included the Neurobehavioral Symptom Inventory, which asks about symptoms during the past 2 weeks without any pre-TBI comparison,[22,23] as well as patient-reported outcomes focusing on specific domains (eMethods 3 in the Supplement). One study objective was to define change scores for the Neurobehavioral Symptom Inventory for further validation. A battery of neurocognitive tests was assessed using the Automated Neuropsychological Assessment Metrics (Automated Neuropsychological Assessment Metrics, version 4, TBI Military

battery).[24,25] Traditional neuropsychological testing results will be published separately.

Outcomes were administered at baseline and after completion of 40 chamber sessions (or at 10 weeks if all sessions were not completed). The PCS questionnaires and the Automated Neuropsychological Assessment Metrics, version 4, were also administered after 20 sessions to explore the number of required sessions. Measures were administered in a standardized order by research coordinators and neuropsychometrists blinded to allocation. The assessment team monitored for symptoms of heightened stress or suicidal thoughts using the University of Washington Risk Assessment Protocol.[26]

Statistical Analysis

This phase 2 trial was designed to enable a preliminary assessment of safety and feasibility, and no formal sample size calculation for efficacy was performed. The change score of at least 2 points on the RPQ-3 subscale (measuring headaches, dizziness, and nausea) was selected to establish a point estimate and refine the sample size requirements for future studies. Allowing for an anticipated dropout rate of 20%, a group size of 24 volunteers was selected to provide sufficient power (>80%) to detect a 50% difference in volunteers achieving that threshold in this pilot study.[21]

Descriptive statistics summarize the population enrolled, including baseline characteristics of each intervention group. Frequencies and percentages are reported for categorical data. Means, medians, and SDs are reported for continuous data. Comparisons of the primary and secondary outcomes were performed using paired *t* test. Change from baseline scores was compared using Wilcoxon signed rank test. The percentage of volunteers achieving a change score of at least 2 points on the RPQ-3 subscale was compared using Fisher exact test. Because this was a phase 2 trial designed to explore outcome measure performance, no correction for multiplicity was performed. Analyses were conducted using statistical software (SAS, version 9.2; SAS Institute). Reported *P* values are 2-sided, and $P < .05$ was considered significant.

Results

Study Population Characteristics

Two hundred eighty-six individuals contacted the hotline, and 190 were referred to the site research teams; 163 service members provided informed consent and were screened, and 72 were eligible and randomized (**Figure**). Enrollment started April 26, 2011, at the following 4 sites: Fort Carson, Colorado; Camp Lejeune, North Carolina; Camp Pendleton, California; and Fort Gordon, Georgia. The last study visit occurred August 24, 2012.

The baseline characteristics of the 3 intervention groups were similar (**Table 1**). The median age was 31 years, 96% were men, and 94% were enlisted. Nineteen percent had a college degree. They had experienced a mean of 3 lifetime concussion events, with the most recent mTBI occurring on average 23 months before randomization. Comorbidities were common. Using the PTSD module of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), 66% met criteria for PTSD. Concurrent interventions for PCS and PTSD showed no difference between groups, although medications were used liberally for pain, sleep, and anxiety. Only 24% had entered into the Department of Defense medical disability process for possible separation from military service.

Two participants experienced an additional mTBI during the 10-week study period. Their data are included in the primary analyses. Eight individuals were unable to complete the study, as outlined in the Figure. In addition, owing to conflicts with medical appointments or work schedules, some participants could not complete all 40 planned chamber sessions within the allotted 10-week period. The number of chamber sessions completed did not differ between the sham and HBO groups (eFigure 1 in the Supplement). All randomized participants were included in the intent-to-treat analysis, while only those completing all 40 chamber sessions and outcomes testing were included in the per-protocol analysis.

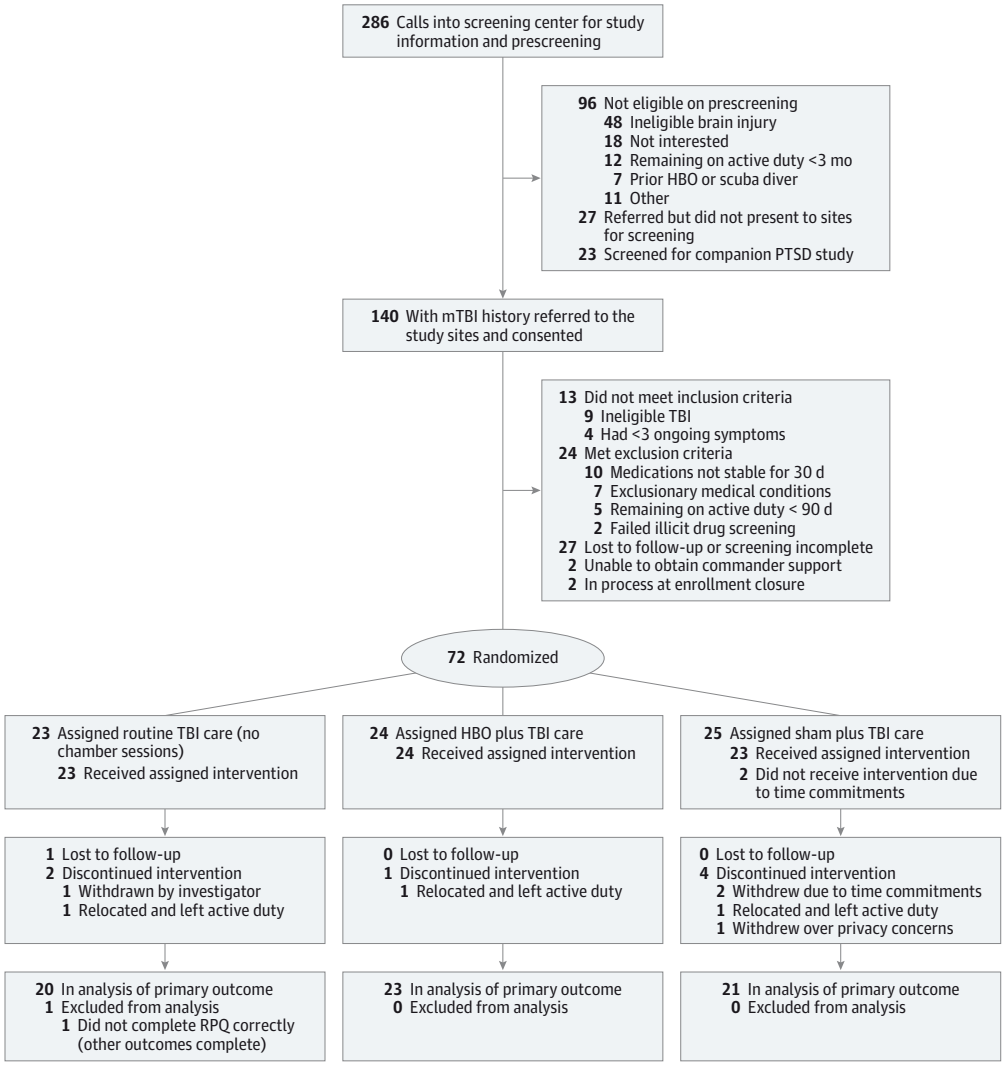
Primary Outcome

The group randomized to no supplemental chamber intervention showed no improvement during the 3-month observational period, with a mean RPQ-3 subscale change score of 0.0 (95% CI, −1.0 to 1.0; $P = .97$) and a mean total RPQ change score of 0.5 (95% CI, −4.8 to 5.8; $P = .91$) (**Table 2**). The group receiving HBO improved symptomatically, with mean change scores of 1.2 (95% CI, 0.0-2.4; $P = .04$) on the RPQ-3 subscale and 5.4 (95% CI, −0.5 to 11.3; $P = .008$) on the total RPQ. The group receiving sham sessions also improved on the RPQ-3 subscale (mean change score, 1.5; 95% CI, 0.1-2.9; $P = .03$) and on the total RPQ (mean change score, 7.0; 95% CI, 1.0-12.9; $P = .02$). Among those in the no chamber intervention group, 25% (95% CI, 11% to 47%) met the prespecified change of at least 2 points on the RPQ-3 subscale. While greater, no meaningful differences ($P = .24$) were detected in the percentage who met the prespecified change of at least 2 points between the HBO group (52%; 95% CI, 33% to 71%) and the sham group (33%; 95% CI, 17% to 55%). Favorable change scores on the total RPQ were higher for the HBO group but no difference between the HBO group and the sham group was observed ($P = .70$). The magnitude of symptom improvement was greater among those who completed all 40 chamber sessions, with no difference ($P = .95$) in change scores between the HBO group (11.0; 95% CI, 3.2-18.8) and the sham group (10.7; 95% CI, 3.9-17.5). An exploratory analysis showed that most improvement occurred within the first 20 chamber sessions of either chamber intervention (eFigure 2 in the Supplement).

Secondary Outcomes

The Neurobehavioral Symptom Inventory scores, measuring concussion-related symptoms during the past 2 weeks, showed slight worsening from baseline in the no chamber intervention group (−1.1; 95% CI, −7.3 to 5.2) compared with the mean symptom improvement after chamber interventions (3.7; 95% CI, −3.7 to 11.2 for the HBO group and 6.9; 95% CI, 1.4-12.4 for the sham group) (**Table 3**). These change scores were not statistically different ($P = .49$). Analysis of the Neurobehavioral

Figure. CONSORT Flow Diagram



HBO indicates hyperbaric oxygen; mTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder; and RPQ, Rivermead Post-Concussion Symptoms Questionnaire.

Symptom Inventory cognitive, affective, and somatic symptom subscales showed no differential clustering of change effects between the 2 chamber interventions. The PTSD symptoms improved after the interventions, favoring the sham group (mean change, 11.4; 95% CI, 5.9-16.9) over the HBO group (mean change, 5.0; 95% CI, −1.7 to 11.6).

The patient-reported outcomes of depression, generalized anxiety, pain, and sleep are listed in **Table 4**. Improvements in change scores trended in favor of the sham group for all measures compared with the HBO group. Health-related quality-of-life outcomes (physical functioning, bodily pain, social functioning, and emotionality domains on the 36-Item Short Form Health Survey [SF-36]) improved, also favoring the sham group over the HBO group. The Global Satisfaction With Life Scale demonstrated similar improvement with both chamber interventions compared with routine PCS care.

No statistical differences were observed between the 2 treatment groups at baseline or on change from baseline scores in any of the cognitive testing measured by the Automated Neuropsychological Assessment Metrics, version 4, standardized throughput scores after 10 weeks. These results are summarized in Table 4.

Two individuals withdrew from the study before chamber sessions were initiated owing to time commitments, leaving safety populations of 24 in the HBO group and 23 in the sham group. The HBO and hyperbaric air sham sessions were well tolerated. No serious adverse events occurred, although 2 adverse events (claustrophobia and worsening of intensity and frequency of headaches) were troubling enough for participants to withdraw from chamber sessions. Fourteen adverse events were attributable to the hyperbaric procedures, equally distributed between the HBO and sham groups (eTable

Table 1. Baseline Characteristics of Eligible Randomized Volunteers[a]

Variable	Standard Care Group (n = 23)	HBO Group (n = 24)	Sham Group (n = 25)
Age, y	30.3 (7.2)	32.5 (7.9)	31.4 (7.6)
Male sex, No. (%)	22 (96)	23 (96)	24 (96)
Highest education, No. (%)			
<High school diploma	0	2 (8)	0
High school diploma	8 (35)	7 (29)	7 (28)
Some college	9 (39)	10 (42)	15 (60)
College degree	5 (22)	2 (8)	3 (12)
Graduate degree	1 (4)	3 (13)	0
Branch of service, No. (%)			
Army	11 (48)	11 (46)	13 (52)
Marines	11 (48)	10 (42)	12 (48)
Navy	0	3 (13)	0
Air Force	1 (4)	0	0
Enlisted, No. (%)	21 (91)	23 (96)	24 (96)
No. of combat deployments	2.6 (1.8)	3.4 (2.7)	3.0 (2.3)
Months since most recent deployment return	12.6 (11.5)	17.1 (15.7)	20.4 (19.0)
Medical disability evaluation board initiated, No. (%)	5 (22)	6 (25)	6 (24)
Participation in Warrior Transition Unit or Wounded Warrior Battalion, No. (%)	4 (17)	2 (8)	5 (20)
Lifetime TBI events	2.8 (2.0)	2.8 (2.0)	3.7 (2.8)
Months since most recent TBI	17.2 (9.8)	24.9 (18.1)	26.3 (16.5)
Common medication use, No. (%)			
SSRI or SNRI	10 (43)	14 (58)	15 (60)
Hypnotic or sleep aid	13 (57)	16 (67)	15 (60)
Daily pain medication	9 (39)	11 (46)	12 (48)
Episodic migraine medication	11 (48)	10 (42)	11 (44)
Fish oil or omega-3 fatty acid	5 (22)	3 (13)	6 (24)
Nonpharmacological intervention, No. (%)			
Counseling or psychotherapy	10 (43)	13 (54)	16 (64)
Cognitive rehabilitation	2 (9)	7 (29)	4 (16)
Baseline postconcussion symptoms			
Total Rivermead Post-Concussion Symptoms Questionnaire score, range, 0-64[b]	32.5 (14.4)	33.0 (15.8)	30.2 (14.2)
Neurobehavioral Symptom Inventory total score, range, 0-88[b]	33.6 (17.6)	34.3 (16.9)	32.6 (16.6)
PTSD comorbidity present by Structured Clinical Interview			
No. (%)	18 (78)	13 (54)	16 (64)
Baseline PTSD Checklist-Civilian Version score, range, 17-85[b]	51.8 (17.5)	48.5 (18.1)	53.5 (18.6)
Alcohol Use Disorders Identification Test-Consumption score, range, 0-12[b]	2.5 (2.9)	2.3 (2.4)	2.8 (4.8)
Test of Memory Malingering retention score ≥45, No. (%)	20 (87)	22 (92)	24 (96)

Abbreviations: HBO, hyperbaric oxygen; PTSD, posttraumatic stress disorder; SNRI, selective noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TBI, traumatic brain injury.

[a] All baseline group comparisons using *t* test had $P > .05$. Continuous variables are shown as means (SDs) unless otherwise noted.

[b] Higher scores reflect more symptoms.

in the Supplement). No participant reported cognitive decline or increased suicidal thoughts.

Discussion

Pilot efficacy trials serve many purposes, including to develop the safety and tolerability of a product, to develop a point estimate for efficacy in the study population for sample size determinations in pivotal trials, and to refine and validate outcomes measures. At times, surprising outcomes data are generated. Our results support the conclusion that supplemental administration of breathing 100% oxygen at 1.5 ATA (HBO procedure) or air at 1.2 ATA (sham procedure) for 60 minutes is well tolerated and improves symptoms and quality of life compared with local care management of PCS without chamber intervention. However, we observed no difference between HBO and sham. We postulate that improvement in the chamber intervention groups was due to placebo effects or the potential benefit of daily interactions with the study staff.

The test article in this study (HBO at 1.5 ATA) increases oxygen tension in plasma to approximately 1000 mm Hg[27] and in brain tissue approximately 3-fold[28] despite oxygen-induced vasoconstriction. The HBO also alters regulation of blood flow

Table 2. Changes From Baseline in Postconcussion Symptom Scores Using the Rivermead Post-Concussion Symptoms Questionnaire and Subscales Among the Intent-to-Treat and Per-Protocol Populations[a]

	Intent-to-Treat Population				Per-Protocol Population		
Intervention	Baseline, Mean (SD)	After Intervention, Mean (SD)	Change Score (95% CI)	*P* Value[b]	Baseline, Mean (SD)	After Intervention, Mean (SD)	Change Score (95% CI)
Rivermead Post-Concussion Symptoms Questionnaire 3 Subscale							
Standard care	5.4 (2.7)	5.1 (2.8)	0.0 (−1.0 to 1.0) (n = 20)	.97	5.4 (2.7)	5.1 (2.8)	0.0 (−1.0 to 1.0) (n = 20)
HBO	5.5 (3.3)	4.2 (3.0)	1.2 (0.0-2.4) (n = 23)	.04	4.7 (3.2)	3.1 (2.2)	1.6 (−0.1 to 3.3) (n = 11)
Sham	4.7 (3.1)	3.5 (3.3)	1.5 (0.1 to 2.9) (n = 21)	.03	4.8 (3.7)	2.7 (2.8)	2.2 (0.7 to 3.6) (n = 13)
Rivermead Post-Concussion Symptoms Questionnaire 13 Subscale							
Standard care	27.1 (12.2)	25.5 (13.9)	0.5 (−4.0 to 5.0)	.87	27.1 (12.2)	25.5 (13.9)	0.5 (−4.0 to 5.0)
HBO	27.5 (13.1)	22.5 (12.4)	4.2 (−0.8 to 9.1)	.02	25.0 (13.4)	15.6 (10.9)	9.4 (2.9 to 15.9)
Sham	25.5 (11.6)	20.7 (12.8)	5.5 (0.7 to 10.3)	.04	25.9 (14.0)	17.4 (13.3)	8.5 (2.8 to 14.2)
Total Rivermead Post-Concussion Symptoms Questionnaire							
Standard care	32.5 (14.4)	30.6 (16.1)	0.5 (−4.8 to 5.8)	.91	32.5 (14.4)	30.6 (16.1)	0.5 (−4.8 to 5.8)
HBO	33.0 (15.8)	26.7 (14.8)	5.4 (−0.5 to 11.3)	.008	29.7 (16.3)	18.7 (13.0)	11.0 (3.2 to 18.8)
Sham	30.2 (14.2)	24.2 (15.4)	7.0 (1.0 to 12.9)	.02	30.8 (17.6)	20.1 (15.7)	10.7 (3.9 to 17.5)

Abbreviation: HBO, hyperbaric oxygen.

[a] The 95% CIs were calculated using 95% binomial exact CIs.

[b] Wilcoxon signed rank test.

for a period thereafter.[15] Anecdotes and case series have described improvements in PCS and PTSD symptoms and cognitive performance after varying numbers of HBO sessions.[13-15,29] Based on these observations, Harch and colleagues[15] postulated that HBO heals the brain, speculating on mechanisms akin to soft-tissue healing of chronic hypoxic diabetic wounds described by Warriner and Hopf.[30] A recent randomized, wait-list, crossover study[29] demonstrated improvements that were owing to aspects of the hyperbaric chamber procedure, although the protocol was not designed to assess if oxygen or other facets of the procedure contributed. Unfortunately, these studies lack adequate control designs to prove that the observed benefits are due to pharmacological effects of HBO rather than nonspecific treatment effects.

This double-blind, randomized clinical study was designed to determine the effect size of the symptomatic improvements by HBO delivered at 1.5 ATA compared with a sham delivery of pressurized room air at 1.2 ATA when supplementing routine mTBI care. A second control group that received mTBI care without chamber intervention was included to evaluate the magnitude of the expected placebo effects from this complex procedure. The design of the procedural blind in studies with self-reported outcomes is critical to managing bias and is described in detail elsewhere.[16]

Taken as a solitary finding in a small multicenter study, concerns about a type II error are valid. However, similar results were obtained in simultaneously conducted, single-site, randomized clinical trials using alternate HBO doses and sham designs.[31-34] Wolf et al[31] also observed improvement in PCS in a military population undergoing 30 chamber sessions at a higher pressure dose than we offered. Volunteers were randomized to receive HBO at 2.4 ATA for 90 minutes or a sham procedure of room air pressurized to 1.3 ATA, slowly falling to 1.2 ATA. Outcome measures included a concussion computerized battery and the Post-traumatic Disorder Check List-Military Version. Postintervention outcomes demonstrated no significant differences in PCS or PTSD symptom improvement. Cifu and colleagues[32] conducted a single-site, dose-ranging study among symptomatic concussed marines who relocated to Pensacola, Florida, for 40 hyperbaric sessions. This 3-group randomized clinical trial evaluated an intervention of daily 2.0 ATA pressurizations of 60 minutes' duration. Volunteers were randomized to 100% oxygen, 75% oxygen (an oxygen tension equivalent to 1.5 ATA used in this study), or 10.5% oxygen (an oxygen tension equivalent to breathing room air at sea level). Overall, modest improvement in symptoms was observed, suggesting that the benefit was not a pressurization effect[32] and that HBO was not superior to oxygen dosing equivalent to room air. No evidence of symptomatic improvement was manifest on reevaluation after 3 months.[33] Likewise, no statistical improvements were observed in neurological, balance, or cognitive outcomes from HBO over those observed in the sham procedure group.[34]

How do we reconcile the anecdotes with the outcomes from a series of small randomized clinical trials? One of the strengths of this study is the inclusion of a routine care PCS group, which allows conclusions to be drawn regarding the observed symptomatic improvement that may occur following participation in daily chamber sessions (HBO or sham) during 8 to 10 weeks in addition to routine mTBI rehabilitation. The

Table 3. Changes From Baseline in Postconcussion and PTSD Symptom Scores Using the Neurobehavioral Symptom Inventory and the PTSD Checklist–Civilian Version and Subscales Among the Intent-to-Treat Population[a]

Symptom Subscale	Standard Care Group (n = 23)	HBO Group (n = 24)	Sham Group (n = 25)
Neurobehavioral Symptom Inventory			
Total score, range 0-88			
Baseline score	33.6 (17.6)	34.3 (16.9)	32.6 (16.6)
Mean (95% CI) change score	−1.1 (−7.3 to 5.2)	3.7 (−3.7 to 11.2)	6.9 (1.4 to 12.4)
Cognitive subscale			
Baseline score	8.0 (4.6)	7.9 (4.4)	7.6 (3.3)
Mean change score	0.6	1.1	1.9
Affective subscale			
Baseline score	13.3 (6.5)	13.0 (7.4)	13.6 (6.4)
Mean change score	−0.5	1.7	3.5
Somatic subscale			
Baseline score	12.2 (8.0)	13.4 (6.6)	11.4 (8.1)
Mean change score	−1.1	1.0	1.5
PTSD Checklist–Civilian Version			
Total score, range 17-85			
Baseline score	51.8 (17.4)	48.5 (18.1)	53.5 (18.6)
Mean (95% CI) change score	2.1 (−2.9 to 7.0)	5.0 (−1.7 to 11.6)	11.4 (5.9 to 16.9)
Reexperiencing subscale			
Baseline score	15.5 (6.1)	13.6 (6.2)	15.3 (5.6)
Mean change score	0.6	1.3	3.1
Avoidance subscale			
Baseline score	19.7 (7.3)	17.9 (7.4)	21.7 (8.8)
Mean change score	1.5	2.0	5.2
Hyperarousal subscale			
Baseline score	16.6 (5.5)	17.0 (5.9)	16.5 (5.5)
Mean change score	0.0	1.7	3.0

Abbreviations: HBO, hyperbaric oxygen; PTSD, posttraumatic stress disorder.

[a] Continuous variables are shown as means (SDs) unless otherwise noted. The 95% CIs are calculated using 95% binomial exact CIs.

observed improvement after chamber sessions is most likely due to placebo responses from the intensive rituals of these repetitive medical procedures. Similar responses have been observed owing to participation in sham acupuncture therapies, which have been associated with substantial response in pain reduction and improved quality of life.[35] Injection placebos are generally more active than pill placebos in migraine investigations.[36] The hyperbaric chamber procedure in a research study is an intense ritual experience consisting of 2 hours of daily social interactions with a dedicated team of nurses and hyperbaric technicians, as well as other participants, in the multiplace hyperbaric chamber. This experience likely triggered a marked placebo response.

It has been argued that the sham designs used in this trial and other Department of Defense studies are not inert and represent dose-ranging trials of pressurized air.[37] We recognize that a sham is not inert, and we cannot completely discount the physiological effects of minimal increases in nitrogen or oxygen from pressurized room air. However, we believe it is biologically implausible that air at 1.2 ATA (equivalent to 2 m of seawater pressure) has a beneficial effect on healing the damaged brain remotely after mTBI. The study by Cifu et al,[32] which varied pressure, oxygen, and nitrogen, demonstrated no dose-response effect to suggest that the sham responses are due to gas or pressure. Placebo responses are more likely, but unfortunately our study was not designed to evaluate the components of a placebo response such as response expectancy, verbal suggestion, and stimulus conditioning.[38] This is an area for further research.

Our trial was not an efficacy trial but rather a pilot study designed to define significant PCS change scores and to determine an effect size to inform sample sizes for potential pivotal trials. The multicenter design improves the generalizability of the findings, but they remain restricted to symptomatic military populations. An additional concern is the absence of validation of a PCS score and defined responsiveness (clinically relevant change scores), but a lack of difference between HBO and sham across all the evaluated domains suggests that the findings are not test specific. A confirmatory trial intended to validate the selected outcome measures is under way (clinicaltrials.gov identifier NCT01611194).

Conclusions

Among service members with PCS, HBO showed no benefits over an air sham compression procedure, but symptoms in both groups improved compared with mTBI care without supplemental chamber interventions. This outcome suggests that the observed improvements were not oxygen mediated but may

Table 4. Baseline Scores and Postintervention Change Scores for Additional Outcome Measures Among the Intent-to-Treat Population

Outcome Measure	Domain and Range	Mean (SD)		
		Standard Care Group (n = 23)	HBO Group (n = 24)	Sham Group (n = 25)
Center for Epidemiologic Studies Depression Scale[a]				
Baseline score	Depression, range 0-60	19.7 (10.5)	16.1 (10.4)	22.6 (13.6)
Mean change score	NA	−0.2 (7.5)	0.0 (12.2)	7.0 (9.7)
Beck Anxiety Inventory[a]				
Baseline score	Anxiety, range 0-63	16.1 (10.5)	16.0 (11.4)	18.3 (13.4)
Mean change score	NA	−1.5 (8.0)	1.1 (9.0)	5.3 (9.1)
Short-Form McGill Pain Questionnaire[a]				
Baseline score	Pain, range 0-45	13.5 (9.3)	14.9 (9.5)	10.7 (7.2)
Mean change score	NA	−0.9 (8.3)	−0.5 (8.8)	2.6 (7.0)
Pittsburgh Sleep Quality Index-Total[a]				
Baseline score	Sleep, range 0-21	11.9 (4.7)	13.0 (4.6)	13.2 (4.2)
Mean change score	NA	−0.6 (3.7)	1.7 (3.6)	2.0 (4.8)
Global Satisfaction With Life Scale[b]				
Baseline score	Global, range 5-35	19.3 (7.5)	19.4 (6.8)	17.5 (7.6)
Mean change score	NA	0.0 (6.0)	2.7 (7.0)	2.6 (6.8)
36-Item Short Form Health Survey[c]				
Physical functioning				
Baseline score	Range 0-100	74.1 (20.5)	69.0 (20.8)	63.8 (28.9)
Mean change score	NA	−2.5 (15.0)	−0.7 (19.6)	10.4 (23.0)
Role-physical				
Baseline score	Range 0-100	33.7 (39.6)	30.2 (32.1)	36.5 (38.3)
Mean change score	NA	−1.3 (23.6)	4.3 (46.9)	16.3 (40.8)
Bodily pain				
Baseline score	Range 0-100	39.6 (23.8)	42.1 (25.1)	44.9 (23.4)
Mean change score	NA	−0.7 (18.8)	−2.0 (20.0)	9.6 (19.7)
General health				
Baseline score	Range 0-100	59.5 (17.2)	52.6 (25.2)	48.8 (16.6)
Mean change score	NA	−1.6 (18.5)	0.8 (28.0)	11.8 (14.9)
Vitality				
Baseline score	Range 0-100	42.2 (25.3)	36.0 (25.2)	32.9 (22.8)
Mean change score	NA	−0.3 (20.6)	7.2 (28.8)	6.8 (18.9)
Social functioning				
Baseline score	Range 0-100	51.1 (24.4)	55.7 (26.8)	47.4 (26.1)
Mean change score	NA	1.9 (17.3)	1.6 (26.4)	15.6 (36.9)
Role-emotional				
Baseline score	Range 0-100	53.6 (45.8)	48.6 (43.9)	44.4 (40.1)
Mean change score	NA	−10.0 (32.6)	0.0 (36.2)	16.7 (51.3)
Mental health				
Baseline score	Range 0-100	59.5 (19.8)	54.7 (23.1)	51.2 (25.5)
Mean change score	NA	−3.0 (13.7)	5.0 (24.5)	5.6 (18.3)
Automated Neuropsychological Assessment Metrics[d]				
Simple reaction time				
Baseline score	Neural processing	77.7 (36.1)	78.3 (34.2)	81.4 (33.5)
Mean change score	NA	−15.0 (25.2)	1.7 (27.8)	1.7 (35.2)
Procedural reaction time				
Baseline score	Processing speed	81.1 (27.4)	88.1 (27.3)	78.6 (30.0)
Mean change score	NA	−4.5 (20.2)	7.2 (24.1)	−8.7 (23.6)

(continued)

Table 4. Baseline Scores and Postintervention Change Scores for Additional Outcome Measures Among the Intent-to-Treat Population (continued)

Outcome Measure	Domain and Range	Mean (SD)		
		Standard Care Group (n = 23)	HBO Group (n = 24)	Sham Group (n = 25)
Code substitution-learning				
Baseline score	Associative learning	90.7 (23.7)	88.0 (20.7)	89.8 (18.7)
Mean change score	NA	−5.4 (13.2)	2.9 (20.3)	−1.0 (19.1)
Mathematical processing				
Baseline score	Working memory	94.0 (16.4)	87.3 (15.0)	84.1 (19.6)
Mean change score	NA	−2.6 (7.6)	3.9 (21.4)	8.1 (25.4)
Matching to sample				
Baseline score	Visuospatial memory	86.0 (15.2)	84.6 (16.6)	87.7 (16.9)
Mean change score	NA	−1.3 (8.7)	6.5 (13.6)	0.4 (22.6)

Abbreviations: HBO, hyperbaric oxygen; NA, not applicable.

[a] Higher scores reflect more intense or frequent symptoms.

[b] Higher scores reflect better satisfaction.

[c] Scores are transformed scores using an age and sex–matched general population. Higher scores reflect better health.

[d] Scores represent the throughput scores (speed and accuracy) standardized to age-matched control subjects.

reflect nonspecific improvements related to placebo effects. Taken with results from other concurrent investigations, our study does not support phase 3 trials of HBO for the treatment of PCS at this time.

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REFERENCES

1. McCrea M, Iverson GL, McAllister TW, et al. An integrated review of recovery after mild traumatic brain injury (MTBI): implications for clinical management. *Clin Neuropsychol*. 2009;23(8):1368-1390.

2. 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;24(1):14-23.

3. Moore DF, Jaffee MS. Military traumatic brain injury and blast. *NeuroRehabilitation*. 2010;26(3):179-181.

4. Peskind ER, Brody D, Cernak I, McKee A, Ruff RL. Military- and sports-related mild traumatic brain

injury: clinical presentation, management, and long-term consequences. *J Clin Psychiatry*. 2013;74 (2):180-188.

5. King NS. Post-concussion syndrome: clarity amid the controversy? *Br J Psychiatry*. 2003;183:276-278.

6. Arciniegas DB, Anderson CA, Topkoff J, McAllister TW. Mild traumatic brain injury: a neuropsychiatric approach to diagnosis, evaluation, and treatment. *Neuropsychiatr Dis Treat*. 2005;1(4):311-327.

7. Belanger HG, Kretzmer T, Vanderploeg RD, French LM. Symptom complaints following combat-related traumatic brain injury: relationship to traumatic brain injury severity and posttraumatic stress disorder. *J Int Neuropsychol Soc*. 2010;16(1): 194-199.

8. Belanger HG, Proctor-Weber Z, Kretzmer T, Kim M, French LM, Vanderploeg RD. Symptom complaints following reports of blast versus non-blast mild TBI: does mechanism of injury matter? *Clin Neuropsychol*. 2011;25(5):702-715.

9. Luethcke CA, Bryan CJ, Morrow CE, Isler WC. Comparison of concussive symptoms, cognitive performance, and psychological symptoms between acute blast-versus nonblast-induced mild traumatic brain injury. *J Int Neuropsychol Soc*. 2011;17(1):36-45.

10. Lange RT, Brickell TA, French LM, et al. Neuropsychological outcome from uncomplicated mild, complicated mild, and moderate traumatic brain injury in US military personnel. *Arch Clin Neuropsychol*. 2012;27(5):480-494.

11. Lange RT, Brickell TA, Ivins B, Vanderploeg RD, French LM. Variable, not always persistent, postconcussion symptoms after mild TBI in U.S. military service members: a five-year cross-sectional outcome study. *J Neurotrauma*. 2013;30(11):958-969.

12. Carlson KF, Kehle SM, Meis LA, et al. Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. *J Head Trauma Rehabil*. 2011;26(2):103-115.

13. Wright JK, Zant E, Groom K, Schlegel RE, Gilliland K. Case report: treatment of mild traumatic brain injury with hyperbaric oxygen. *Undersea Hyperb Med*. 2009;36(6):391-399.

14. Harch PG, Fogarty EF, Staab PK, Van Meter K. Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. *Cases J*. 2009;2:6538.

15. 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;29(1):168-185.

16. 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;39(4):807-814.

17. Weaver LK, Dicks C, Deru K, Miller RS. Regulatory considerations for a traumatic brain injury (TBI) indication for hyperbaric oxygen (HBO2). *Undersea Hyperb Med*. 2013;40(5):439-441.

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

19. Weaver LK, Churchill SK, Bell J, Deru K, Snow GL. A blinded trial to investigate whether "pressure-familiar" individuals can determine chamber pressure. *Undersea Hyperb Med*. 2012;39 (4):801-805.

20. 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;242(9):587-592.

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

22. Cicerone KD, Kalmar K. Persistent postconcussion syndrome: the structure of subjective complaints after mild traumatic brain injury. *J Head Trauma Rehabil*. 1995;10(3):1-17.

23. Caplan LJ, Ivins B, Poole JH, Vanderploeg RD, Jaffee MS, Schwab K. The structure of postconcussive symptoms in 3 US military samples. *J Head Trauma Rehabil*. 2010;25(6):447-458.

24. Reeves D, Kane R, Winter K, Raynsford K, Pancella T. *Automated Neuropsychological Assessment Metrics (ANAM): Test Administrator's Guide*. 1.0 ed. St Louis: Missouri Institute of Mental Health; 1993.

25. Vincent AS, Bleiberg J, Yan S, et al. Reference data from the Automated Neuropsychological Assessment Metrics for use in traumatic brain injury in an active duty military sample. *Mil Med*. 2008; 173(9):836-852.

26. Reynolds SK, Lindenboim N, Comtois KA, Murray A, Linehan MM. Risky assessments: participant suicidality and distress associated with research assessments in a treatment study of suicidal behavior. *Suicide Life Threat Behav*. 2006; 36(1):19-34.

27. Weaver LK, Howe S, Snow GL, Deru K. Arterial and pulmonary arterial hemodynamics and oxygen delivery/extraction in normal humans exposed to hyperbaric air and oxygen. *J Appl Physiol (1985)*. 2009;107(1):336-345.

28. Rockswold SB, Rockswold GL, Zaun DA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. *J Neurosurg*. 2010;112(5):1080-1094.

29. 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. doi:10.1371/journal.pone .0079995.

30. Warriner RA, Hopf HW. Enhancement of healing in selected problem wounds. In: Gesell LB, ed. *Hyperbaric Oxygen Therapy Indications*. Durham, NC: Undersea and Hyperbaric Medical Society; 2008.

31. 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; 29(17):2606-2612.

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

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

34. 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*. 2013;28(5):420-432.

35. Linde K, Niemann K, Schneider A, Meissner K. How large are the nonspecific effects of acupuncture? a meta-analysis of randomized controlled trials. *BMC Med*. 2010;8:75.

36. de Craen AJ, Tijssen JG, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol*. 2000;247(3):183-188.

37. 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.

38. Kong J, Spaeth R, Cook A, et al. Are all placebo effects equal? placebo pills, sham acupuncture, cue conditioning and their association. *PLoS One*. 2013; 8(7):e67485. doi:10.1371/journal.pone.0067485.