Hyperbaric Oxygen for Blast-Related Postconcussion Syndrome: Three-Month Outcomes

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Objective: Mild traumatic brain injury (mTBI) and postconcussion syndrome (PCS) are common among military combatants. Hyperbaric oxygen (HBO_2) is a proposed treatment for these conditions, but it has not been rigorously studied. The objective of this study was to determine the effects of HBO2 by 3 months post compression at 2 commonly employed dosing levels to treat PCS; whether specific subgroups may have benefited; and if no overall effect was found, whether benefit is masked by other conditions.

Methods: This randomized, double-blind, sham-controlled study was conducted at the Naval Air Station in Pensacola, Florida on 61 male Marines with a history of mTBI and PCS. Intervention consisted of 40 once daily 60-minute hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA) at 1 of 3 randomly preassigned oxygen fractions, resulting in respective blinded groups with an oxygen-breathing exposure equivalent to (1) surface air (sham), (2) 100% oxygen at 1.5ATA, or (3) 100% oxygen at 2.0ATA. The main outcome measure was the Rivermead Post-Concussion Questionnaire-16 (RPQ-16) collected before compressions and at 2 later points.

Results: The interaction of time by intervention group was not significant for improvement on the RPQ-16. Nor was there evidence of efficacy on the RPQ-16 for any subgroup. No significant time by intervention interaction was found for any functional, cognitive, or psychomotor secondary outcome measure at an unadjusted 0.05 significance level.

Interpretation: Using a randomized control trial design and analysis including a sham, results showed no evidence of efficacy by 3 months post-compression to treat the symptomatic, cognitive, or behavioral sequelae of PCS after combat-related mTBI.

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The United States has reported nearly 250,000 deployment-related mild traumatic brain injuries (mTBIs) in the Global War on Terrorism (GWOT).[1] Many of these individuals have chronic symptoms consistent with postconcussion syndrome (PCS). Irritability, sleep disturbance, forgetfulness, anxiety, headaches, poor concentration, and other symptoms are reported years after mTBI among GWOT veterans.[2–6] Blast-induced mTBI has been especially common and may further alter risk of PCS and distribution of individual symptoms,[6–9] particularly when repetitive.[2,10] Comorbidities often complicate PCS as well[6,11,12]; most GWOT veterans with mTBI have chronic pain, post-traumatic stress disorder (PTSD), depression, and/or other mental health conditions,[13] possibly explaining the higher rate of PCS in military personnel.[13,14]

mTBI sequelae extend beyond symptom distress. Neurocognitive impairment, pervasive after moderate or severe TBI,[15–18] can persist after mTBI.[19–22] Balance deficits are common after mTBI in both civilian and

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military samples.[23–27] Fine motor speed and dexterity impairment is also common after TBI, and its assessment is recommended by the National Institute of Neurologic Disorders and Stroke (NINDS).[28]

The large number of veterans and service members (SMs) suffering from PCS has led to standardized programs of mTBI evaluation and treatment in respective health care systems. But standard treatment remains a symptom-based approach, as there are no proven medications or other interventions to treat the underlying brain injury. One proposed but unproven intervention is hyperbaric oxygen (HBO_2), the breathing of high levels of oxygen at an increased pressure at least 1.4× greater than the atmospheric absolute pressure at sea level.[29] Proposed mechanisms of action by which exposure to hyperoxygenated blood imparts neurologic recovery include reactivation of damaged but functionally retrievable neurons along metabolic or electrical pathways[30]; stem cell mobilization to sites of injury; immune modulation; and having impact on fundamental neurotransmitters.[31]

The Department of Defense (DoD) and Veterans Affairs (VA) have developed a clinical research initiative assessing the utility and efficacy of HBO_2,[32] including this 3-arm, randomized, double-blinded, sham-controlled trial of SMs with mTBI and PCS comparing the effects of 2 hyperbaric oxygen-breathing dosing regimens. Analyses of a 1 week postcompression regimen in this trial revealed no efficacy for the primary outcome measure, which was PCS symptoms as measured by the Rivermead Post-Concussion Questionnaire-16 (RPQ-16)[33] or on cognitive/psychomotor performance.[34] The current analyses investigated potential delayed or progressive response to HBO_2 at 3 months, whether participant attributes masked efficacy, and whether efficacy was specific to subgroup(s). A repeated measures statistical model, including multiple explanatory variables, was used to analyze PCS symptoms and secondary outcomes. We hypothesized that HBO_2 would lead to improvements in symptoms, function, and cognition/psychomotor performance over time. We further hypothesized that efficacy was specific for or masked by select participant attributes, such as PTSD status or age.

Subjects and Methods

The Defense Advanced Research Projects Agency and US Navy Bureau of Medicine and Surgery sponsored this single-center, randomized, 3-arm, sham-controlled, double-blinded trial of HBO_2 exposure for PCS after mTBI. This study received all institutional review board and governmental approvals. Sample size estimates were calculated using a 10% difference for the primary outcome, which has been reported to be a clinically meaningful improvement.[35] Inclusion criteria included diagnosis of mTBI occurring within the past 3 months to 3 years,[36] diagnosis of PCS, 2 months of stable psychiatric status, 1 month of stable psychotropic medication history, and ability to undergo testing. The diagnoses of mTBI and PCS were confirmed through interview, physical examination, and review of medical records. Exclusions included previous exposure to or contraindications to hyperbaric exposure (such as air-trapping pulmonary conditions). Recruitment was primarily from Marine Corps Base Camp Lejeune, North Carolina. Recruitment involved standard techniques, including open, in-person information sessions with medical personnel on the project, medical clinic flyers posted for both medical personnel and potential subjects, medical clinic brochures displayed for both medical personnel and potential subjects, and direct calls to base command and medical leadership requesting identification and access to all potentially eligible subjects.

Using computer-generated random numbers, participants were block randomized to 1 of 3 conditions in the hyperbaric chamber (40 total exposures). To ensure subject and investigator blinding to specific treatment exposures, subjects were pressurized inside the chamber to 2.0 atmospheres absolute (ATA). Subjects breathed an oxygen–nitrogen gas blended to achieve the oxygen pressure equivalents to which they were assigned. Three gas mixtures were employed: (1) sham air equivalent of 10.5% oxygen (balance 89.5% nitrogen), (2) 1.5ATA oxygen equivalent of 75% oxygen (balance 25% nitrogen), and (3) 2.0ATA oxygen equivalent of pure oxygen (0% nitrogen); these are respectively referred to as sham air, 1.5ATA O2, and 2.0ATA O2. Once at 2.0ATA of pressure, each subject breathed the assigned gas mixture for 60 minutes. Exposures were delivered using modifications of established protocols in the US Navy Diving Manual and through consultation with the Navy Bureau of Medicine and Surgery, Undersea Medicine and Radiation Health.[31,37] Intervention dosing used in this study was chosen based on consensus opinion of the DoD and VA.[32] Further details on methods of HBO_2 delivery, sham delivery, blinding, and exposures are reported elsewhere.[33]

Outcome Measures

Outcome measures were collected pre-exposure (Pre), within the first week following last exposure (Post-1), and at 3 months following the last exposure (Post-2). Administration time for the battery of self-report and cognitive and psychomotor testing was approximately 5 hours. RPQ-16 is a widely used Likert-type symptom inventory of 16 items evaluating somatic, cognitive, and emotional symptoms.[35] RPQ-16 is an NINDS-recommended outcome measure for mTBI and is analyzed using total score (range = 0–84), with higher values indicative of more severe symptoms. Two subscales are described, with items 1 to 3 constituting the RPQ-3 and remaining 13 items constituting the RPQ-13.[35]

Multiple, prespecified, secondary outcomes were obtained measuring participants' neuropsychological, psychomotor, functional, and behavioral health. Cognitive performance measures were chosen for high sensitivity to attention, memory, processing speed deficits, and efficiency of administration. Selected

tests were: Conners' Continuous Performance Test-II (CCPT-II),[38] Paced Auditory Serial Addition Test (PASAT),[39] Halsted-Reitan Trail Making Test A and B,[40] Stroop Color-Word Interference test,[41] California Verbal Learning Test-II (CVLT-II),[42] Wechsler Adult Intelligence Scale III (WAIS-III) select items,[43] Delis-Kaplan Executive Function Systems version of the Controlled Oral Word Association Test (COWAT),[44] and Benton Visual Memory Test-Revised (BVMT-R).[45] All selected tests are recommended by NINDS TBI Comprehensive Evaluation Common Data Elements. Psychometric properties are available on the NINDS website.[28] Given the expansive neuropsychological subtest results, we prespecified a leading outcome for each cognitive domain of interest: verbal fluency (COWAT Letter Fluency), executive function (Trails B), working memory (WAIS-III Working Memory Index[46]), visual attention (Stroop Color-Word Interference), sustained visual attention (CCPT-II Detectability Index), auditory attention (PASAT 2.0 pacing), delayed verbal memory (CVLT Delayed Free Recall[47]), and delayed visual memory (BVMT-R Delayed Free Recall). Except for WAIS and CCPT-II index scores, neuropsychological test raw scores were analyzed.

The fine motor speed/dexterity aspect of psychomotor performance was measured using the Grooved Pegboard test.[48] Balance was measured using computerized posturography on a dual-plate force platform, the Smart Balance Master (NeuroCom International, Clackamas, OR), via the composite equilibrium score on the Sensory Organization Test,[49] a weighted average of equilibrium scores across 6 sensory conditions and index of overall performance.

Behavioral well-being was assessed with RPQ-16 subscales, RPQ-3 and RPQ-13, and the Center for Epidemiological Studies Depression Scale.[50] Functional status was measured across 3 domains using TBI outcome measures: global outcome using the Glasgow Outcome Scale Extended,[51] life activities participation using the Mayo Portland Adaptability Inventory-4 Participation Index,[52] and life satisfaction using the Satisfaction with Life Scale.[53]

Explanatory Variables

Select explanatory covariates previously shown or theorized to influence mTBI outcome were included in the analysis. Dichotomous variables were: self-reported, past mTBIs before deployment (Yes, No); number of military blast exposures categorized as Low (<4) versus High (≥4); time since worst blast exposure categorized as Recent (<6 months) versus Old (>6 months); loss of consciousness (LOC) and/or post-traumatic amnesia (PTA) after the subject's worst mTBI (Yes, No); PTSD at baseline using the traditional PTSD Check-List[54,55] cutoff of 50 or above (Yes, No)[56]; feigned or invalid effort testing on the Test of Memory Malingering at any data collection point using traditional criteria (Pass, Fail);[57] and alcohol misuse via the Alcohol Use Disorders Identification Test[58] categorized as At-Risk (≥4) versus Not At-Risk (<4).[58] Scale explanatory variables included: age in years; bodily pain on the Short Form McGill Pain Questionnaire, a validated self-rating of sensory and affective pain descriptors[59]; and estimated premorbid intellectual functioning, assessed using the Wechsler Test of Adult Reading (WTAR).[60,61]

Statistical Methods

After performing descriptive statistics, a repeated measures mixed-effect model was used to determine efficacy for the primary outcome: whether RPQ-16 scores differed between intervention groups (sham air, 1.5ATA O2, 2.0ATA O2) across time points (Pre, Post-1, Post-2). This model included all of the explanatory variables listed, as well as time (Pre, Post-1, Post-2), intervention group (sham air, 1.5ATA O2, 2.0ATA O2), and the interaction between time and intervention group. Evidence of intervention efficacy was determined if the parameters corresponding to the interaction term were nonzero at the 0.05 level. This model was adjusted for following subjects longitudinally, through an unstructured covariance structure and a random effect accounting for the cohort.

Several secondary analyses were conducted with similar models. Like the primary analysis, evidence of efficacy was defined as a significant interaction between time and treatment group. Lastly, to assess whether the active intervention was superior to sham for a specific subgroup (ie, participants with or without PTSD) with regard to the primary outcome, a model was fit with time, intervention group, and each covariate, along with all 2-way and the prespecified 3-way interactions. All secondary effects were also evaluated at the 0.05 level. SAS version 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Participant Characteristics

The consort flow diagram is shown in Figure 1. Primary reasons for exclusion were nonconfirmation of mTBI diagnosis, active medication changes, and/or schedule conflicts. One of the consenting but ineligible (moderate severity TBI) SMs requested and was permitted to enter the trial, but was excluded from analysis. The 61 final, fully eligible participants were distributed among intervention arms as follows: 21 in sham air, 21 in 1.5ATA O2, and 19 in 2.0ATA O2.

All participants within the final sample were male, with a mean age of 23.3 years (standard deviation [SD] = 3.24). Twenty (33%) were married, 3 (5%) were divorced, and 38 (62%) were single. All were Marines, and 97% had E1 to E6 pay grades. Analysis of variance (ANOVA) and chi-square analysis revealed no between-group differences with respect to age, pay grade, or marital status. All deployment-related mTBIs were caused by blast (for those with >1 mTBI, blast caused the worst); 85% were from an improvised explosive device, 3.0% were from a rocket-propelled grenade, 1.7% were from mortar attack, and 10% were not categorizable. Baseline assessments occurred a mean of 8.5 months (SD = 6.6 months, range = 3–39 months) after most recent deployment-related mTBI.

As previously reported, symptom severity on the RPQ-16 was high at baseline,[33] and none of the outcome

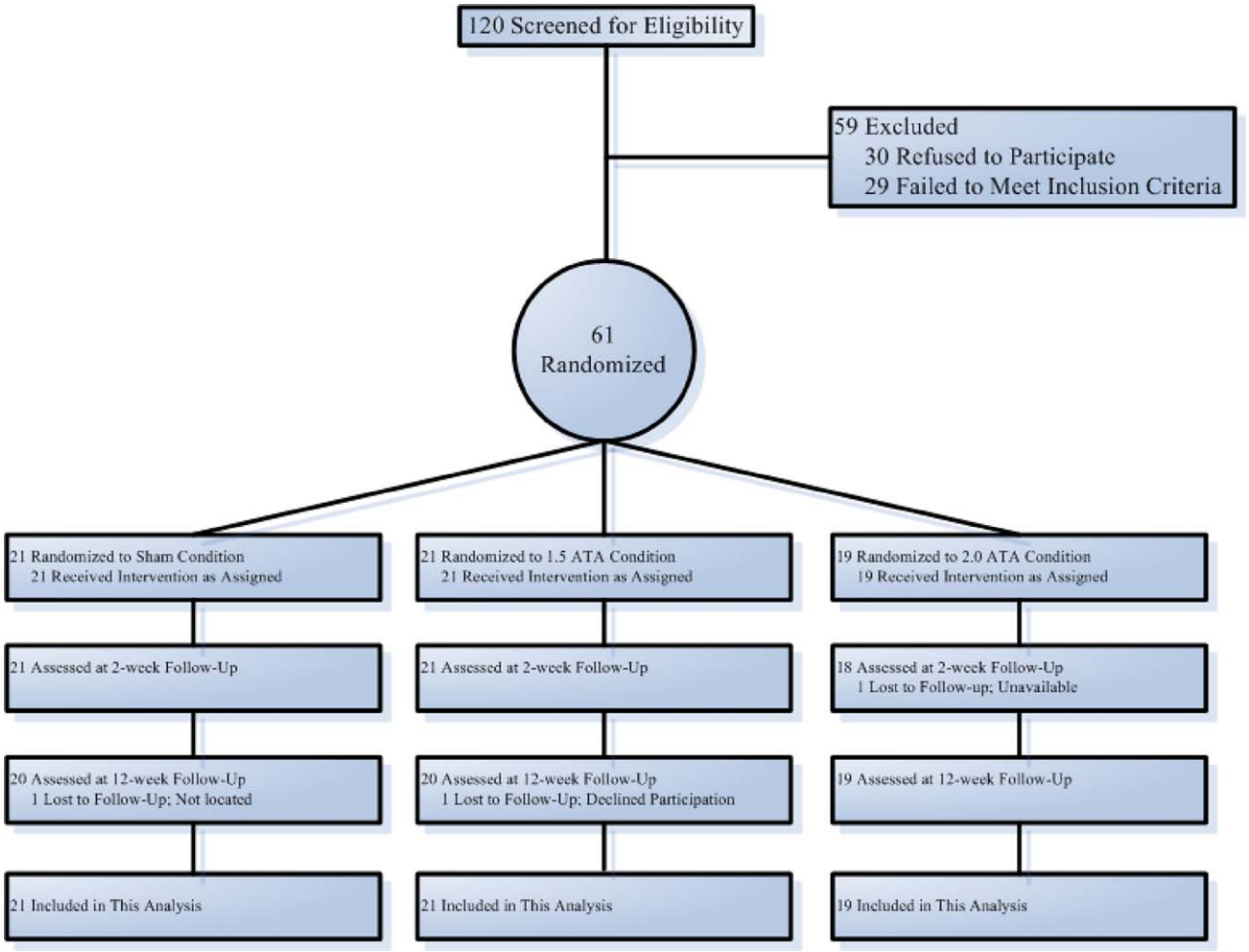

FIGURE 1: Participant selection and randomization. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

measures' distributions at baseline differed between intervention groups.[33,34] The distribution of explanatory variables by group at baseline is shown in Table 1; no between-groups differences were found (chi-square for categorical, ANOVA for scale, all $p > 0.05$).

Main Analysis for Primary Outcome (RPQ-16)

Main effects of each RPQ-16 explanatory variable are shown in Table 2. Significant main effects were found for PTA, PTSD, and pain levels (McGill). Not considering secondary interactions with other explanatory variables, such as intervention group or time point effects, subjects whose worst mTBI resulted in PTA (or LOC) had higher RPQ-16 scores versus those without ($d = 6.61$, standard error [SE] = 3.00, 95% confidence interval [CI] = 0.57–12.64). Similarly, those with PTSD at baseline had higher RPQ-16 scores ($d = 6.06$, SE = 2.24, 95% CI = 1.55–10.56) than those without. Participants with higher pain levels had worse RPQ-16 scores, with mean RPQ-16 increasing by 0.58 (SE = 0.10, 95% CI = 0.38–0.78) per unit increase on the McGill. No other explanatory variables were significantly related to RPQ-16 scores.

The statistical test for efficacy, measuring any interaction between intervention group (sham air, 1.5ATA O2, 2.0ATA O2) difference on RPQ-16 score across any time points (Pre, Post-1, Post-2), was not significant ($F_{4,63.7} = 1.0$, $p = 0.410$). Intervention group RPQ-16 by time is plotted in Figure 2.

Secondary Outcomes Analyses

Results of statistical testing of efficacy for each secondary outcome, the respective mixed model treatment group by time interaction, are shown in Table 3. No secondary outcomes showed a significant difference over time between the 3 intervention groups (all $p > 0.05$).

Although not relevant to assessing intervention efficacy, some secondary outcome analyses did show significant effect(s) with 1 or more explanatory variables similar to the primary outcome. The following secondary measures demonstrated statistically significant changes irrespective of treatment. Improvements were shown on Trails B (at 12

TABLE 1. Explanatory Variable Distribution by Intervention Group

Variable	Level	Sham	1.5ATA O2	2.0ATA O2	*p*
Blast exposure	High (≥4)	8 (38%)	8 (38%)	6 (32%)	0.887
	Low (<4)	13 (62%)	13 (62%)	13 (68%)	
LOC	Yes	8 (38%)	12 (57%)	6 (32%)	0.231
	No	13 (62%)	9 (43%)	13 (68%)	
PTA	Yes	13 (62%)	15 (71%)	8 (42%)	0.161
	No	8 (38%)	6 (29%)	11 (58%)	
PTSD	Yes (PCL ≥ 50)	6 (29%)	6 (29%)	10 (53%)	0.359
	No (PCL < 50)	15 (71%)	15 (71%)	9 (47%)	
TOMM	Pass	19 (90%)	18 (86%)	14 (74%)	0.340
	Fail	2 (10%)	3 (14%)	5 (26%)	
Time elapsed	≤6 months	11 (52%)	9 (43%)	11 (58%)	0.627
	>6 months	10 (48%)	12 (57%)	8 (42%)	
Drinking status	High risk	11 (52%)	11 (52%)	11 (58%)	0.923
	Low risk	10 (36%)	10 (48%)	8 (42%)	
Previous head injury	Yes	3 (15%)	6 (32%)	7 (33%)	0.349
	No	17 (85%)	13 (68%)	14 (67%)	
Age, yr		24 (1.2)	22.9 (2.9)	22.9 (3.3)	0.326[a]
WTAR, baseline, mean [SD]		33.9 [6.1]	32.9 [6.5]	34.0 [6.0]	0.828[a]
McGill score, baseline, mean [SD]		11.9 [8.3]	12.0 [6.0]	10.4 [8.8]	0.780[a]

Percentages are calculated as percentage of each treatment arm. Probability values correspond to Pearson chi-square tests, unless indicated otherwise.
Calculated from an *F*-statistic.
ATA = atmospheres absolute; LOC = loss of consciousness; PCL = PTSD Check-List; PTA = post-traumatic amnesia; PTSD = post-traumatic stress disorder; SD = standard deviation; TOMM = Test of Memory Malingering; WTAR = Wechsler Test of Adult Reading.

weeks), CVLT (at 2 weeks), PASAT (at 2 and 12 weeks), BVMT (at 12 weeks), and COWAT (at 2 and 12 weeks), whereas WAIS-III working memory worsened (at 2 weeks). No significant changes were noted on any of the other secondary outcome measures. Complete results of the effects are shown in Supplementary Tables A1 to A17.

Subgroup Analyses for the Primary Outcome

A model was fit with time, intervention, and each explanatory variable, along with all 2-way and the prespecified 3-way interactions to test for any intervention effect within specific participant groups (ie, PTSD-positive and -negative groups) with respect to the RPQ-16. None of the 3-way interactions was significant at the 0.05 level (Table 4). Thus, there was no evidence of efficacy on the primary outcome for any of the subgroups examined.

Discussion

This collaborative randomized, double-blinded, sham-controlled trial studying the effects of HBO_2 on PCS after mTBI shows nonefficacy for either 1.5ATA or 2.0ATA equivalent oxygen-breathing exposures on PCS symptom severity at 3 months postcompression. We also found no evidence that efficacy was masked by any of the explanatory variables and no evidence of efficacy within any of the subgroups we defined. We likewise found no evidence of treatment efficacy for any of the secondary outcomes. This is despite comprehensive testing with measures known to be sensitive to the subtle impairments that are typical of mTBI and PCS, such as indices of complex attentional control,[62,63] delayed recognition memory,[47,64] memory proactive interfence,[63] and computerized posturography, and despite running all 16 secondary outcome models at an unadjusted alpha = 0.05 level, which increased the odds of spurious findings from type 1 error.

Analyses showed several significant explanatory variable main effects for both the primary RPQ-16 outcome and the secondary outcomes. Not considering treatment

TABLE 2. Explanatory Variable Main Effects on Rivermead Post-Concussion Questionnaire-16

Explanatory Variable	*F*-Ratio (*df*1, *df*2)	*p*
Time	0.9 (2, 55.5)	0.426
Intervention group	0.5 (2, 47.2)	0.590
Blast exposure	2.6 (1, 48.2)	0.112
PTA	4.8 (1, 48.4)	0.033[a]
LOC	0.9 (1, 48.1)	0.350
PTSD	7.3 (1, 48.5)	0.009[a]
Injury elapse	2.4 (1, 48.3)	0.131
Alcohol use	1.5 (1, 129)	0.219
Age	0.0 (1, 50.1)	0.925
Previous head injury	0.0 (1, 48.1)	0.937
McGill	33.4 (1,143)	<0.001[a]
WTAR	1.2 (1,119)	0.278
TOMM	0.1 (1, 47.7)	0.730

[a]Explanatory variables having a $p < 0.05$.
LOC = loss of consciousness; PTA = post-traumatic amnesia; PTSD = post-traumatic stress disorder; TOMM = Test of Memory Malingering; WTAR = Wechsler Test of Adult Reading.

TABLE 3. Hypothesis Tests for the Treatment by Time Interaction for the Secondary Outcomes

Predictor	*F*-Ratio (*df*1, *df*2)	*p*
RPQ-3	0.7 (4, 64.0)	0.592
RPQ-13	1.0 (4, 63.8)	0.400
Mayo	0.6 (4, 62.8)	0.702
Balance, SOT	1.0 (4, 58.9)	0.443
WAIS	1.8 (4, 59.4)	0.141
Trail-Making B	0.7 (4, 64.9)	0.621
Stroop	0.6 (4, 60.2)	0.664
CPT-II	0.6 (4, 60.9)	0.685
CVLT Long Delay Free Recall	0.8 (4, 63.1)	0.523
PASAT	1.4 (4, 52.9)	0.256
BVMT Delay Recall	0.5 (4, 62.3)	0.753
COWAT	1.6 (4, 64.1)	0.197
Grooved Peg Board	0.5 (4, 47.5)	0.724
SWLS	0.5 (4, 61.2)	0.751
Depression, CESD	0.5 (4, 63.8)	0.767
GOSE	0.8 (4, 57.7)	0.503

BVMT = Benton Visual Memory Test; CESD = Centers for Epidemiological Studies Depression Scale; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; CVLT = California Verbal Learning Test; GOSE = Glasgow Outcome Scale Extended; PASAT = Paced Auditory Serial Addition Test; RPQ = Rivermead Post-Concussion Questionnaire; SOT = Sensory Organization Test; SWLS = Satisfaction With Life Scale; WAIS = Wechsler Adult Intelligence Scale.

group or time point, RPQ scores were higher for participants with PTA after their worst mTBI, active PTSD, or greater pain levels. For secondary outcomes, the scattered significant main effects findings included: (1) poorer life activities participation for those with greater levels of pain and greater time elapsed from injury date, (2) poorer balance for those with LOC (worst mTBI) and those with lower WTAR, (3) better working memory for those with higher WTAR, and (4) poorer delayed visual memory for those with PTSD. Secondary outcomes analyses showed significant interactions for the main effect of time. For the entire cohort, there was improvement over time for working memory, executive function, delayed verbal memory, delayed visual memory, and verbal fluency. But improvement over time was not accompanied by a significant intervention group by time interaction for any measure and therefore cannot be attributed to HBO_2 exposure. The lack of converging temporal improvement on any of the numerous symptom or functional measures suggest that these findings may be better explained by practice effects or other explanations, such as natural recovery, placebo effect, or the nonspecific

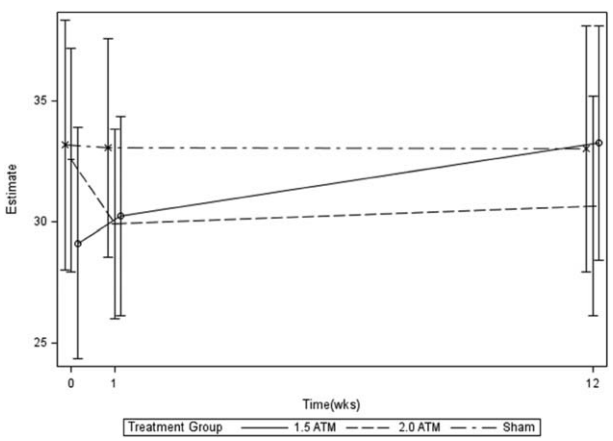

FIGURE 2: Rivermead Post-Concussion Questionnaire-16 (RPQ-16) by intervention group over time (baseline, 1 week, 3 months). Time by intervention group effect: $F_{4,63.7} = 1.0$, $p = 0.410$.

TABLE 4. Hypothesis Tests for Subgroup Efficacy Analysis

Explanatory Variable	*F*-Ratio (*df*1, *df*2)	*p*
Blast exposure	0.57 (4, 62.8)	0.685
PTA	1.00 (4, 62.9)	0.416
LOC	0.20 (4, 63.4)	0.938
PTSD	0.13 (4, 63.9)	0.971
Injury elapse	0.67 (4, 63.1)	0.618
Alcohol use	0.27 (4, 65.4)	0.898
Age	0.78 (4, 69.3)	0.539
Previous head injury	2.06 (4, 62.1)	0.097
McGill	0.12 (4, 72.6)	0.975
WTAR	0.67 (4, 69.1)	0.618
TOMM	0.83 (4, 66.5)	0.510

Rivermead Post-Concussion Questionnaire-16 outcome; 3-way interaction between explanatory variable, time, and treatment group.
LOC = loss of consciousness; PTA = post-traumatic amnesia; PTSD = post-traumatic stress disorder; TOMM = Test of Memory Malingering; WTAR = Wechsler Test of Adult Reading.

effects of attention and care in the context of study participation. This would also support the notion that the subjects were interested in finding ways to improve their difficulties, and thus not a population that was biased against a positive outcome.

This investigation was part of a series of federally funded, coordinated research trials to assess the efficacy of HBO_2 for persistent symptoms after mTBI, so that the VA and/or DoD could implement treatment programs based on scientific rigor.[32] The VA and DoD medical heath systems have been established to rapidly and systematically implement any and all scientifically valid and clinically useful modalities to attenuate the sequelae of combat. A study strength is the incorporation of features lacking in prior studies outside of the DoD's current coordinated program,[32] including randomization, blinding, control groups, and multiple HBO_2 dose levels to assess dose–response effects. A carefully designed sham control, with all participants receiving the same compression intensity, was employed to ensure effective blinding. By adjusting the oxygen/nitrogen ratio, 3 well-disguised groups were achieved, equivalent to (1) breathing surface air (sham), (2) 100% oxygen at 1.5ATA, or (3) 100% oxygen at 2.0ATA. An additional strength is the use of a mixed-effect model to confer extra statistical control over potential interactions between participant characteristics and outcomes. Use of this design allowed assurance against efficacy being masked by 1 or multiple known influencers of mTBI outcome. This provided a platform to explore for subgroup efficacy; however, none was found for the primary outcome.

The multitude and breadth of analyses of secondary outcomes and covariates in this study could be considered a weakness due to our analysis of multiple (n = 16) outcomes without adjusting alpha levels. This approach was taken due to the pilot nature of the study, but it weakens confidence where differences were found. The significant covariant and secondary outcome main interactions noted are subject to increased threat of type 1 error. These findings should be considered preliminary and needing further empirical confirmation. Despite this, there was a set of results whose recurring pattern made type 1 error unlikely: the improvement over time in multiple cognitive performance measures irrespective of treatment group. This pattern is consistent with findings in a separate small (n = 16) uncontrolled trial of HBO_2 for PCS, in which Harch et al[65] reported improvement in full-scale intelligence quotient, Weschler Memory Scale (WMS) IV Delayed Memory, WMS-IV Working Memory, Stroop Test, Test of Variables of Attention (TOVA) Impulsivity, TOVA Variability, and Grooved Pegboard 1 week after 1.5ATA HBO_2. Harch et al's lack of a sham control restricted analyses to within-group differences only, so as with the current study, these findings cannot be interpreted as evidence of intervention efficacy. Furthermore, even in a published trial without sham control, Churchill et al failed to find any efficacy from HBO_2 in individuals with brain injury.[66]

This study had several other inherent limitations. The sample was exclusively male, so findings may not be generalizable to females. Small sample size limits the power of the study. Due to the high number of outcomes, there also were some randomly missing data points, including 3 missed follow-up evaluations. The mixed-effect model allowed us to incorporate subjects who did not complete a given measurement point and include all subjects in all statistical tests. Secondary gain was not directly measured, but could have introduced participant selection bias, as study participation was associated with extended time away from military assignment.

In conclusion, this study found no beneficial effect of HBO_2 exposure 3 months postcompression for symptoms, functional status, or cognitive or psychomotor performance at either 1.5 or 2.0ATA equivalent oxygen breathing compared to sham intervention. Within-group changes were noted for the entire sample in both primary and secondary (neuropsychological testing) measures, and interactions were noted between primary and secondary

measures and within secondary measures; however, none of these were noted to be related to HBO_2.These results parallel those of Wolf et al[31] and do not support the use of HBO_2 to treat PCS after combat-related mTBI even at typical treatment pressures advocated by hyperbaric clinicians for mTBI.[65,67]

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Authorship

W.C.W. and D.X.C. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C.W.G. was responsible for the data analysis.

Potential Conflicts of Interest

Nothing to report.

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