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Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial

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Abstract

Persistent postconcussion syndrome (PPCS) after mild traumatic brain injury (mTBI) is a significant public health and military problem for which there is limited treatment evidence. The aim of this study was to determine whether forty 150 kPa hyperbaric oxygen therapies (HBOTs) can improve symptoms and cognitive function in subjects with the PPCS of mTBI, using a randomized controlled crossover design with 2-month follow-up. Sixty-three civilian and military subjects with mTBI/PPCS were randomized to either 40 HBOTs at 150 kPa/60 minutes, once daily, 5 days per week in 8 weeks or an equivalent no-treatment control period. The Control Group was then crossed over to HBOT.

Subjects underwent symptom, neuropsychological, and psychological testing, before and after treatment or control with retesting 2 months after the 40th HBOT. Fifty subjects completed the protocol with primary outcome testing. HBOT subjects experienced significant improvements in Neurobehavioral Symptom Inventory, Memory Index, Automated Neuropsychological Assessment Metrics, Hamilton Depression Scale, Hamilton Anxiety Scale, Post-Traumatic Stress Disorder Checklist, Pittsburgh Sleep Quality Index, and Quality Of Life after Brain Injury compared to the Control Group. After crossing over to HBOT the Control Group experienced near-identical significant improvements. Further improvements were experienced by both groups during the 2-month follow-up period. These data indicate that 40 HBOTs at 150 kPa/60 minutes demonstrated statistically significant improvements in postconcussion and Post-Traumatic Stress Disorder symptoms, memory, cognitive functions, depression, anxiety, sleep, and quality of life in civilian and military subjects with mTBI/PPCS compared to controls. Improvements persisted at least 2 months after the 40th HBOT. The study was registered on ClinicalTrials.gov (NCT02089594) on March 18, 2014 and with the U.S. Food and Drug Administration under Investigational New Drug #113823. The Institutional Review Boards of the United States Army Medical Research and Materiel Command Office of Research Protections Human Research Protection Office and the Louisiana State University School of Medicine (approval No. 7381) approved the study on May 13, 2014 and December 20, 2013, respectively.

Keywords: chronic brain injury, hyperbaric oxygen therapy, neurobehavioral symptom inventory, neuropsychological testing, neurorehabilitation, persistent postconcussion syndrome, post-traumatic stress disorder, randomized controlled trial, symptoms, traumatic brain injury

INTRODUCTION

Mild traumatic brain injury (mTBI)/persistent postconcussion syndrome (PPCS) is a significant public health and military problem. In 2013 there were 2.8 million emergency department visits, hospitalizations, or deaths in the United States due to TBI,1 75% of which are estimated to be mild TBI.2 When non-hospital non-emergency department visits for head trauma are included there were an additional 1.16 million adult (18–64 years old)3 and 845,000 pediatric cases,4 comprising approximately 50% of all head trauma cases in the U.S. In total there appears to be at least 4.8 million TBI cases annually in the U.S., 4.1 million of which are mild TBI. This figure is further increased by military service

members and the elderly non-emergency department/hospital TBI subsets and is orders of magnitude higher worldwide.

Historically, only 15% of mild TBI patients are diagnosed with the PPCS,5 but more recent literature suggests a rate as high as 55%5 for mTBI with loss of consciousness. The longer the symptoms persist the higher the likelihood that they will become permanent. When symptoms persist longer than 3 years the syndrome appears to be permanent.6,7 In a military veteran population nearly 70% of patients entering the Veterans Administration system with a diagnosis of TBI were still receiving treatment 4 years later.7 Treatment has consisted of psychoeducational interventions, cognitive rehabilitation, psychotherapeutic approaches, integrated behavioral health interventions, and psychoactive medication administration. There is some evidence to support the use of cognitive rehabilitation approaches,8 limited evidence for the other three non-pharmacologic interventions,8 and very little evidence for psychoactive medications.9 This is a pharmacologic study which employed a well characterized biological wound-healing therapy, hyperbaric oxygen therapy (HBOT), to treat the chronic brain wounds of mTBI.10

HBOT is the use of increased atmospheric pressure and hyperoxia as drugs to treat disease pathophysiology11 through gene expression and suppression.12 Treatment effects are a function of dose and timing of intervention in the disease process.13 HBOT doses of 200–300 kPa have been applied to a limited 15 reimbursed acute central nervous system and acute or chronic extremity wound and infection diagnoses in the U.S.14,15 while a much larger list of diagnoses have been treated internationally.16,17,18 Lesser doses have been used mainly for chronic neurological conditions.13

HBOT has been applied to chronic TBI in animals and humans since 198919,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41 with apparent conflicting results.25,27 Various researchers have attributed the different results in mTBI PPCS to mischaracterized sham groups/the effects of different doses of HBOT,11,12,24,42,43,44,45,46,47 design differences,48 (small sample size, dissimilar outcome measures/populations/sites/protocol adherence, non-equivalence of group, selection bias),29 ritual experience,28 and placebo/Hawthorne effects.49 Regardless, all of the studies performed at 150 kPa of oxygen in mTBI/PPCS have generated positive data.22,24,26,28,29,39,40 The purpose of this study was to use a randomly assigned Treatment Group versus Control Group design to demonstrate

efficacy and confirm or refute the previous experience using the 150 kPa oxygen dose of HBOT.

SUBJECTS AND METHODS

Full details of the Methods and Protocol are in **Additional file 1**.

Design

Subjects were randomly assigned to Treatment Group or Control Group; the Control Group then crossed over to receive HBOT following the control period (**Figure 1**). There was no sham control group in this study. Due to the bioactivity of oxygen and hydrostatic pressure,11,12,50 the two active components of an HBOT,11,12 the requirement of the absence of these two components for a true sham51 HBOT,11,12 and the absence of successful demonstration of a true sham HBOT in the history of clinical HBOT, a first-ever true sham HBOT control group was not attempted in this efficacy trial.

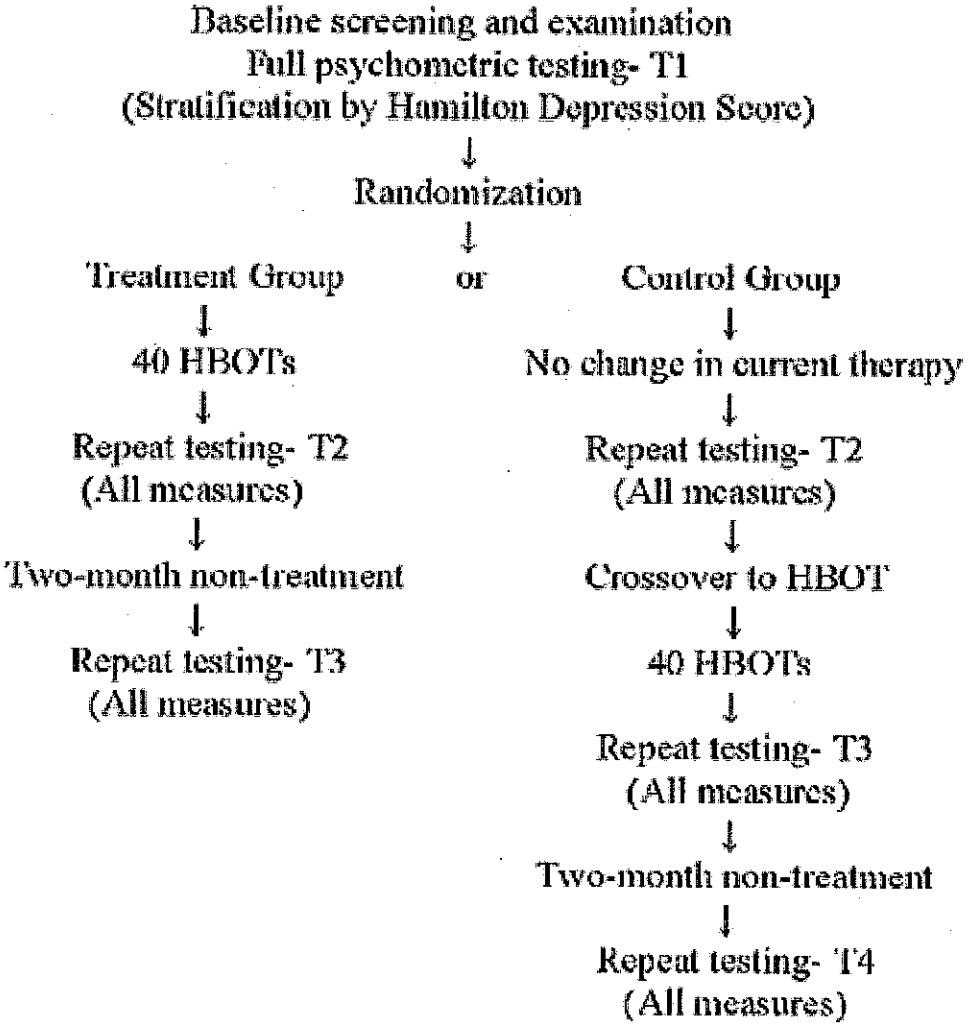

Figure 1

Study flow chart.

Note: HBOT: Hyperbaric oxygen therapy; T1–4: test points 1–4.

The outcome data was primarily generated by the study neuropsychologist who was blinded to group designation (single-blind). The study was registered on ClinicalTrials.gov (NCT02089594) on March 18, 2014 and with the U.S. Food and Drug Administration under Investigational New Drug #113823. The Institutional Review Boards of the United States Army Medical Research and Materiel Command Office of Research Protections Human Research Protection Office and the Louisiana State University School of Medicine (approval No. 7381) approved the study on May 13, 2014 and December 20, 2013, respectively. The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement.

Subjects

Subjects were 18–65 year old adults who had experienced one or more blunt or blast mTBIs, as defined by the American Congress of Rehabilitation Medicine mTBI definition,52 that was at least 6 months old (3 months longer than the minimum time limit for definition of PPCS),53 occurred on or after September 11, 2001, resulted in the symptoms of the PPCS54 that developed within 4 weeks after the mTBI, and were continuously present through to enrollment. Subjects had to score at least 2255 on the Neurobehavioral Symptom Inventory (NSI)56 and complain of headache, a marker of symptomatic mTBI in both military57 and civilian populations58 with equal incidence in blast and blunt mTBI.59

Screening procedure and neuropsychological outcome testing

Subjects were screened with the NSI, Michigan Alcohol Screening Test,60 Drug Abuse Screening Test,61 Post-Traumatic Stress Disorder Check List-Military or Civilian (PCL-M or C 4: score less than 50),62 Ohio State TBI Identification Method63 structured interview, Clinician Administered PTSD Scale64 if the PCL was ≥ 50, semi-structured psychiatric evaluation, in-depth medical history by the principal investigator, and effort testing with complete neuropsychological outcome test battery [Test of Memory Malingering,65 Green Word Memory

Test,66 Wechsler Test of Adult Reading,67 Hamilton Depression Scale (HAM-D),68 Hamilton Anxiety Scale (HAM-A),69 Wechsler Adult Intelligence Scale (WAIS-IV)70 or Wechsler Abbreviated Scale of Intelligence,71 Wechsler Memory Scale,72 Rey Auditory Verbal Learning Test Delayed Recall (RAVLT),73 Benton Visual Retention Test (BVRT),74 Stroop Test,75 Controlled Oral Word Association Test,76 Category Fluency Test (Animals Test),77 Automated Neuropsychological Assessment Metrics (ANAM-4.1 A-1746T Core version),78 Pittsburgh Sleep Quality Index (PSQI),79 and Quality of Life after Brain Injury (QOLIBRI)].80 Subjects were then stratified by the HAM-D score and randomized to either the control (Control Group) or HBOT (Treatment Group) treatment using a block randomization scheme with random block sizes of four, six, or eight implemented in the R programming language.

Postconcussion symptoms were measured using the NSI. Cognitive functions were measured by five categorical variables constructed to reduce the data plus three additional measures (RAVLT-Delayed Recall, the ANAM-4.1, and Benton Visual Retention Test). The five categorical variables were: 1) Working Memory Index, 2) Memory Index, 3) Executive Function Index using T-scores,81 4) Information Processing Speed Index, and 5) General Intellectual Ability (See **Additional file 2** for index construction). The behavioral/emotional changes were measured using the HAM-D, HAM-A, PSQI, the QOLIBRI, and the PCL-C or PCL-M. The NSI and Working Memory Index were chosen as co-primary outcomes for the study82,83,84,85 and sample size determined by prior data in veterans24 and control group effects.86

Hyperbaric treatment

Forty treatments at 150 kPa for 60 minutes without air breaks were delivered consecutively in Class B Sechrist Industries (Anaheim, CA, USA) monoplace chambers (Model 2500 or 3200) once a day, 5 days per week.

Statistical analysis

The primary analysis compared the mean difference in the 14 outcome variables between the two treatment groups (Control and HBOT) from test point 1 to test point 2 using a general linear model and a two-sample *t*-test. Paired samples *t*-tests were used to assess changes within treatment groups from test point 1 to each subsequent time point for all 14 outcome variables. For categorical baseline variables chi-squared tests of homogeneity were used

to test for differences in proportions across categories among groups. Analyses were performed using SAS 9.4 (SAS, Cary, NC, USA).

RESULTS

Quantitative analysis of mild traumatic brain injury persistent postconcussion syndrome patients

Recruitment began on May 13, 2014, ended on September 29, 2017, and the last subject completed 2-month follow-up testing on March 5, 2018. Subject enrollment and testing numbers are in **Figure 2**. Only 12/13 in the Dropout Group were included in the demographic analysis (**Tables 1** and **2**) since one subject dropped out due to an employer problem, later re-enrolled, and was re-randomized to Control Group. That subject was counted in the Control Group for demographic analysis. Three of the thirteen Dropouts occurred pre-randomization due to an undisclosed post-enrollment discovered disqualifying neurological diagnosis, failed effort testing, and failed urine drug test. Eight of the ten remaining dropouts were in the Treatment Group and two in the Control Group. Four of the eight patients in Treatment Group Dropouts occurred before any treatment was delivered (one could not stay for immediate treatment, two could not obtain work releases for treatment, and one was diagnosed with cancer the day of randomization), one occurred after the third HBOT (financial problems) and one after the first HBOT (principal investigator missed the positive drug test). The other two Treatment Group Dropouts did not report for post-treatment testing. The remaining two Dropouts (Control Group) self-removed from the study due to substance abuse relapse/entry to an inpatient rehabilitation program and deterioration in symptoms upon returning to Canada post-randomization. Five subjects did not complete 40 HBOTs: four due to late fatigue (30, 34, 39, and 39 HBOTs) and one due to a pre-scheduled flight home (39 HBOTs). Thirty Clinician Administered PTSD Scales, based on a PCL over 50 during prescreening, were administered out of the 63 subjects who were enrolled in the study. None were found to have clinical PTSD at the time of enrollment.

Figure 2

CONsolidated Standards Of Reporting Trials (CONSORT) diagram.

Note: HBOT: hyperbaric oxygen therapy.

Table 1

Demographic variables: Analysis of group equivalence at baseline (test point 1) for the Treatment Group with HBOT first, Control Group, and Dropout Group

Demographic variables	Treatment Group (*n* = 23)	Control Group (*n* = 27)	Dropout Group (*n* = 12)	*P*-value
Age (yr)	42.7±10.7(22–58)	42.3±11.2(22–60)	42.3±10.8(27–59)	0.897
Years education	14.0±3.1(8–18)	15.6±1.95(10–20)	15.9±2.6(13–20)	0.030
Wechsler Test of Adult Reading Intelligence Quotient (Scaled Score)	108.7±9.2(88–122)	110.7±6.59(92–121)	114.5±5.37(100–122)	0.385
Number TBIs in lifetime	4.3±6.2(1–30)	3.6±3.22(1–15)	3.6±3.4(1–11)	0.646
Time index TBI to enrollment (d)	1598.1±1099 (194.0–1303.0)	1748.6±1471.7 (234.0–4460.0)	1767.3±868.8 (325.0–3568.0)	0.891
Time screen to enrollment (d)	84.5±71.4(16–320)	60.5±58.2(17–305)	51.1±17.7(12–74)	0.197
Test of Memory Malingering 2 (total correct)	49.4±1.5(45–50)	49.9±0.77(46–50)	50.0±0.0(50–50)	0.163
Word Memory Test Consistency (%)	92.6±7.5(77.5–100)	90.5±10.6(60–100)	90.6±6.0(80–100)	0.421
Word Memory Test Delay Recall (%)	95.2±5.9(80–100)	93.1±9.4(65–100)	93.5±7.94(75–100)	0.345
Word Memory Test Immed Memory (%)	94.7±6.6(77.5–100)	92.6±7.98(72.5–100)	93.8±4.2(85–100)	0.326
Sex (% female)	52.2%(12/23)	63%(17/27)	41.7%(5/12)	0.444
Race (% Caucasian)	95.7%(22/23)	88.9%(24/27)	91.7%(11/12)	0.411
Blast *vs*. Blunt (% Blunt)	87.0%(20/23)	92.6%(25/27)	83.3%(10/12)	0.325
Civil *vs*. Military (% Military)	17.4%(4/23)	18.5%(5/27)	33.3%(4/12)	0.918
Loss of consciousness (% yes)	73.9%(17/23)	66.7%(18/27)	83.3% (10/12)	0.551
Alcohol (% any use)	65.2%(15/23)	44.4%(12/27)	66.7%(8/12)	0.142
Clinician Administered Post-Traumatic Stress Disorder	47.8%(11/23)	40.75%(11/27)	66.7%(8/12)	0.615
Scale (% administered)				
Magnetic resonance imaging brain (% normal)	72.7%(16/23)	59.3%(16/27)	41.7%(5/12)	0.318
Tobacco (% no use)	73.9%(17/23)	77.8%(21/27)	66.7%(8/12)	0.75

Note: Data are expressed as the mean ± SD (range) in age, years education, Wechsler Test of Adult Reading Intelligence Quotient, number TBIs in lifetime, time index TBI to enrollment, time screen to enrollment, Test Of Memory

Malingering 2, Word Memory Test Consistency, Word Memory Test Delay Recall, and Word Memory Test Immed Memory, and percent in others. Data among all the three groups are analyzed by Tukey's test. *There are no significant differences among any of the 3 pairs of groups. Dropout Group: Subjects who dropped out of the study; TBI: traumatic brain injury; test point 1: baseline.

Table 2

Outcome variables: Analysis of group equivalence at baseline for the Treatment Group with hyperbaric oxygen therapy first, Control Group, and Dropout Group

Outcome variables	Treatment Group (*n* = 23)	Control Group (*n* = 27)	Dropout Group (*n* = 12)	*P*-value
Neurobehavioral Symptom Inventory (total score)	39.0±9.6	44.6±11.8	34.1±9.1	0.029*
	37 (24–58)	44 (21–67)	34 (22–48)	
Working Memory Index (SS)	103.5±12.2	104.6±14.4	109.2±10.9	0.466
	103 (78–127)	106 (79–131)	106.3 (89–128)	
Memory Index (SS)	101.7±14.3	102.9±14.3	97.8±11.1	0.574
	100 (75–127)	104 (72–107)	95.3 (79–124)	
Information Process Speed Index (SS)	94.0±14.5	95.4±15.0	98.3±13.3	0.709
	94 (62–117)	97 (65–122)	100 (71–122)	
Executive Function Index (T score)	45.3±8.8	48.1±7.1	47.3±7.9	0.461
	44 (30–60)	47 (37–64)	47 (36–59)	
Wechsler Adult Intelligence Scale Full Scale	105.6±12.3	106.4±10.6	106.9±10.3	0.942
Intelligence Quotient (SS)	108 (80–130)	106 (89–128)	107 (89–123)	
Automated Neuropsychological Assessment	−1.84±1.0	−1.6±1.3	−1.11±0.87	0.195
Metrics (composite score)	−1.72 (−4.2 to −0.2)	−1.3 (−3.9–0.6)	−1.2 (−2.7–0.2)	
Hamilton Depression Scale (total)	15.2±5.0	14.4±7.5	15.8±8.6	0.849
	16 (6–24)	15 (0–26)	15.5 (3–30)	
Hamilton Anxiety Scale (total)	16.5±7.9	15.8±7.3	17.5±10.4	0.835
	17 (2–35)	16 (4–31)	17 (0–32)	
Quality of Life after Brain Injury (composite score)	40.3±12.4	38.9±16.3	42.3±16.9	0.813

Outcome variables	Treatment Group (n = 23)	Control Group (n = 27)	Dropout Group (n = 12)	P-value
	40 (21–63)	38 (8–85)	40 (15–73)	
Pittsburgh Sleep Quality Index (composite score)	11.9±4.0	10.5±4.9	12.3±4.8	0.405
	12 (5–19)	11 (2–20)	12 (5–21)	
Benton Visual Retention Test (#correct)	7.3±1.5	7.0±1.9	7.2±1.5	0.812
	8 (4–10)	8 (3–10)	7.5 (3–9)	
Rey Auditory Verbal Learning Test Delay	47.8±14.0	47.1±14.6	41.3±9.3	0.365
Recall (T score)	50 (24–65)	47 (25–67)	42 (24–57)	
Post-Traumatic Stress Disorder Check List (total)	37.9±12.1	39.7±13.2	31.6±9.5	0.252
	37 (20–67)	37 (19–68)	32 (19–48)	

Note: Data are expressed as the mean ± SD, median (range). *Neurobehavioral Symptom Inventory was significantly different among the three groups. The Tukey's test showed that the Control and Dropout Groups were significantly different, but the Treatment and Control Groups were not. Dropout Group: Subjects who dropped out of the study; SS: scaled scores.

Demographics of the sample and dropout analysis

Analyses of group equivalence at baseline for demographic variables and outcome variables are presented for the Treatment, Control and Dropout Groups in **Tables 1** and **Table 2**. Tukey's Test87 analysis of the two significantly different variables (years of education and NSI) showed no significant difference between any two groups for years of education while the NSI was significantly different between the Control and Dropout Groups. The Dropout subjects had significantly lower symptom scores than the Control Group, but the two main study groups (Treatment and Control Groups) did not differ in PPCS complaints on the NSI.

Changes in the outcome after HBOT *vs.* control period

Figure 3 graphs the change in the two co-primary outcome variables (NSI and Working Memory Index) for the control (Control Group) *vs.* HBOT (Treatment Group) and the proportionate domain changes for NSI in the Treatment Group. The Treatment Group experienced a 26.3-point decrease in the NSI PPCS

symptom score compared to a 2.5-point decrease in the Control Group ($P < 0.0001$). The cognitive domain of the Treatment Group NSI registered the greatest relative improvement with a 19% relative decrease. The difference between the groups in working memory change was not significant. In total eight of the 14 outcome variables were significantly improved in the Treatment Group compared to control (Control Group): PPCS symptoms (NSI), Memory Index, overall cognitive efficiency (ANAM 4), depression (HAM-D), anxiety (HAM-A), quality of life (QOLIBRI), sleep quality (PSQI), and post-traumatic anxiety symptoms (PCL) (**Table 3**).

Figure 3

Change in the Neurobehavioral Symptom Inventory (NSI) and Working Memory Index for the Control Group *vs.* Treatment Group and the proportionate domain changes for NSI in the Treatment Group.

Note: (A) Change in primary outcome measures (post-HBOT minus pre-HBOT or post-control minus pre-control). $N = 23$ for Treatment Group and 27 for Control Group. (B) Treatment Group domain contributions to total NSI score pre- and post-HBOT. The components of the NSI are the somatic-vestibular (S-V), affective (A) and cognitive (Cog).

Table 3

Effect of pre-to-post-hyperbaric oxygen therapy change for Treatment Group versus pre-to-post control period for Control Group

Outcome variables	TP1 to TP2 mean change (TP2 minus TP1)		Mean difference	*P* of group difference
	Treatment Group ($n = 23$)	Control Group ($n = 27$)		
Neurobehavioral Symptom Inventory (total score)	39.0 to 12.7=–26.3	44.6 to 42.1=–2.5	–23.9±9.22(–29.2 to –18.6)	0.0001
Working Memory Index (SS)	103.5 to 111.0=+7.5	104.6 to 110.6=+6	1.5±6.5(–2.23–5.13)	0.431
Memory Index (SS)	101.7 to 113.3=+11.6	102.9 to 107.6=+4.7	6.92±8.6(2.01–11.83)	0.0067
Information Processing Speed Index (SS)	94.0 to 102.5=+8.5	95.4 to 100.7=+5.3	3.14±9.4(–2.25–8.54)	0.247

Outcome variables	TP1 to TP2 mean change (TP2 minus TP1)		Mean difference	*P* of group difference
	Treatment Group (*n* = 23)	Control Group (*n* = 27)		
Executive Function Index (T score)	45.3 to 47.0=+1.7	48.1 to 47.8=–0.3	1.97±5.8(–1.36–5.28)	0.2384
Wechsler Adult Intelligence Scale Full Scale Intelligence Quotient (SS)	105.6 to 112.2=+6.6	106.4 to 110.9=+4.5	1.13± 5.76(–1.16–5.41)	0.1993
Automated Neuropsychological Assessment Metrics (composite score)	–1.84 to –1.02=+0.82	–1.6 to –1.3=+0.3	0.51±0.64(0.15–0.88)	0.0069
Hamilton Depression Scale (total)	15.2 to 7.5=–7.7	14.4 to 12.8=–1.6	–5.99±6.85(–9.89 to –2.08)	0.0034
Hamilton Anxiety Scale (total)	16.5 to 9.3=–7.2	15.8 to 14.7=–1.1	–6.19±7.48(–10.5 to –1.92)	0.0054
Quality of Life after Brain Injury (composite score)	40.3 to 58.5=+18.2	38.9 to 40.9=+2.0	16.8±14.9(8.2–25.44)	0.0003
Pittsburgh Sleep Quality Index (composite score)	11.9 to 9.0=–2.9	10.5 to 10.9=+0.4	–3.31±3.64(–5.39 to –1.24)	0.0024
Benton Visual Retention Test (#correct)	7.3 to 7.3=0.0	7.0 to 7.3=+0.3	–0.22±1.72(–1.2–0.76)	0.6517
Rey Auditory Verbal Learning Test Delay Recall (T score)	47.8 to 52.3=+4.5	47.1 to 47.0=–0.1	4.6±11.9(–2.19–11.44)	0.1785
Post-Traumatic Stress Disorder Check List (total)	37.9 to 26.0=11.9	39.7 to 37.5=2.2	13.2±11.2(8.6–17.7)	0.0001

Note: Data in Mean difference column are mean change between Treatment Group and Control Group mean changes, and are analyzed using a two-sample *t*-test. SS: Scaled scores; TP1: test point 1 (baseline); TP2: test point 2.

Sequential changes for each group's 14 outcome variables at all test points are shown in **Tables 4** and **5**. The Treatment Group experienced significant improvements in 11 of 14 outcome tests after HBOT (**Table 4**) *vs.* 5 of 14 tests for the Control Group during the control period; the RAVLT showed a near significant improvement ($P = 0.0515$) while Executive Function was insignificantly changed in the Treatment Group. After HBOT the Control Group had a significant improvement in 13 out of 14 variables (**Table 5**) that were nearly identical in magnitude to the same Treatment Group test domain changes. Both groups showed minor changes in the RAVLT while neither group

demonstrated improvement in the Benton Visual Retention Test. After HBOT there were no significant differences in any outcome change between groups.

Table 4

Treatment Group change from pre-to-post-hyperbaric oxygen therapy and follow-up for outcome variables (postconcussion symptoms, cognitive, and emotional)

Outcome variables	**Baseline (T1) (*n* = 23)**	**Post-HBOT (T2) (*n* = 23)**	***P*-value (T1 vs. T2)**	**2-mon follow-up (T3) (*n* = 20)**	***P*-value (T1 vs. T3**
Neurobehavioral Symptom Inventory (total)§	39.0±9.6	12.7±10.6	0.0005	18.7±13.3	< 0.0001
	37 (24–58)	11 (0–44)		18.5 (1–47)	
Working Memory Index (SS)	103.5±12.2	111.0±8.8	< 0.0001	113.7±11.5	< 0.0001
	103 (78–127)	113 (95–127)		114 (90–138)	
Memory Index (SS)	101.7±14.3	113.3±11.6	< 0.0001	120±11.9	< 0.0001
	100 (75–127)	113 (89–135)		120 (93–140)	
Information Processing Speed Index (SS)	94.0±14.5	102.5±12.9	0.0001	104.2±14.7	0.0002
	94 (62–117)	102 (81–127)		102 (81–132)	
Executive Function Index (T score)	45.3±8.8	47.0±8.2	0.121	51.5±7.5	0.0001
	44 (30–60)	45 (33–61)	53 (36–66)		
Wechsler Adult Intelligence Scale Full	105.6±12.3	112.2±9.5	< 0.0001	117.2±11.7	< 0.0001
Scale Intelligence Quotient (SS)	108 (80–130)	114 (97–136)	117 (96–145)		
Automated Neuropsychological	–1.84±1.0	–1.02±0.8	< 0.0001	–1.1±1.4	< 0.001
Assessment Metrics (composite score)	–1.72 (–4.2 to –0.2)	–0.95 (–2.78–1.21)	–0.7 (–4.24–1.35)		
Hamilton Depression Scale (total)§	15.2±5.0	7.5±4.6	< 0.0001	6.3±5.3	< 0.0001
	16 (6–24)	6 (0–15)	5 (0–17)		
Hamilton Anxiety Scale (total)§	16.5±7.9	9.3±5.6	< 0.0001	7.1±6.7	< 0.0001
	17 (2–35)	10 (0–24)	5 (0–24)		
Quality Of Life after Brain Injury (composite score)	40.3±12.4	58.5±17.6	< 0.0001	62.1±16.0	< 0.0001

Outcome variables	Baseline (T1) (*n* = 23)	Post-HBOT (T2) (*n* = 23)	*P*-value (T1 vs. T2)	2-mon follow-up (T3) (*n* = 20)	*P*-value (T1 vs. T3
	40 (21–63)	63 (30–98)	12		
Pittsburgh Sleep Quality Index (composite score)§	11.9±4.0	9.0±3.8	0.0002	8.0±4.6	0.0006
	12 (5–19)	8 (3–15)	8 (2–16)		
Benton Visual Retention Test (#correct)	7.3±1.5	7.3±1.8	n.s.	7.6±1.8	n.s.
	8 (4–10)	7 (4–10)	8 (4–10)		
Rey Auditory Verbal Learning Test	47.8±14.0	52.3±8.8	0.0515	51.8±10.6	n.s.
Delay Recall (T score)	50 (24–65)	53 (32–67)	54 (28–67)		
Post-Traumatic Stress Disorder Check	37.9±12.1	26.0±8.3	< 0.0001	27.1± 11.7	0.0005
List (total) §	37 (20–67)	24 (16–45)	25 (3–51)		

Note: Data are expressed as Mean ± SD, median (range), and are analyzed by paired samples *t*-tests. Scores are reported in standard scores, T-score format, or Manual scoring. Increasing scores indicate improvement except those marked with §. n.s.: No significance; T1–3: test points 1–3.

Table 5

Control Group change from pre-to-post-control, -hyperbaric oxygen therapy, and follow-up for outcome variables (postconcussion symptoms, cognitive, and emotional)

Outcome variables	Baseline (T1) (*n* =27)	Post control (T2) (*n* =27)	*P*-value (T1 *vs.* T2)	Post-HBOT (T3) (*n* =27)	*P*-value (T2 *vs.* T3)	2-mon follow-up (T4) (*n*=23)	*P*-value (T2 *vs.* T4)
Neurobehavioral Symptom Inventory (total)§	44.6±11.8	42.1±10	n.s.	16.5±12.7	< 0.0001	19.8±14.3	< 0.0001
	44 (21–67)	41 (26–62)		14 (0–44)		18 (0–48)	
Working Memory Index (SS)	104.6±14.4	110.6±14.9	0.0001	115.2±15.1	0.001	118.6±15.	0.0001
	106 (79–131)	113 (82–140)		117 (84–140)		124 (86–147)	
Memory Index (SS)	102.9±14.3	107.6±13.0	0.006	118.3±14.5	< 0.0001	122.7±14.5	< 0.0001

Outcome variables	Baseline (T1) (*n* =27)	Post control (T2) (*n* =27)	*P*-value (T1 *vs.* T2)	Post-HBOT (T3) (*n* =27)	*P*-value (T2 *vs.* T3)	2-mon follow-up (T4) (*n*=23)	*P*-value (T2 *vs.* T4)
	104 (72–107)	108 (84–132)		120 (88–143)		126 (81–143)	
Information Processing Speed Index (SS)	95.4±15.0	100.7±17.1	0.004	107.4±15.0	0.004	109.9±16.8	0.002
	97 (65–122)	105 (71–132)		111 (74–127)		108 (74–146)	
Executive Function Index (T score)	48.1±7.1	47.8±6.8	n.s.	52.9±9.4	< 0.0001	51.5±10.2	0.01
	47 (37–64)	48 (37–61)		54 (37–73)		51 (37–78)	
Wechsler Adult Intelligence Scale Full	106.4±10.6	110.9±11.8	< 0.0001	117.0±11.5	< 0.0001	119.8±12.6	< 0.0001
Scale Intelligence Quotient (SS)	106 (89–128)	111 (92–136)		121 (94–139)		121 (94–139)	
Automated Neuropsychological	−1.6±1.3	−1.3±1.5	0.008	−0.7±1.1	< 0.0001	−0.8±1.4	0.03
Assessment Metrics (composite score)	−1.3 (−3.9–0.6)	−1.0 (−4.5–0.9) 。		−0.6 (−3.7–0.8)		−0.7 (−3.4–1.8)	
Hamilton Depression Scale (total)§	14.4±7.5	12.8±7.6	n.s.	6.6±6.6	0.0002	6.7±6.9	0.0002
	15 (0–26)	11 (2–27)		5 (0–23)		4 (0–22)	
Hamilton Anxiety Scale (total)§	15.8±7.3	14.7±7.3	n.s.	7.4±6.3	< 0.0001	8.5±8.0	0.0001
	16 (4–31)	15 (0–28)		5 (0–20)		6 (0–31)	
Quality of Life after Brain Injury (composite score)	38.9±16.3	40.9±14.8	n.s.	62.5±23.1	< 0.0001	62.0±21.3	< 0.0001
	38 (8–85)	40 (5–75)		68 (8–99)		63 (10–100)	
Pittsburgh Sleep Quality Index (composite score)§	10.5±4.9	10.9±4.2	n.s.	7.4±4.7	0.0001	7.9±5.4	0.0006
	11 (2–20)	12 (3–19)		7 (1–20)		7 (0–21)	
Benton Visual Retention Test (#correct)	7.0±1.9	7.3±2.3	n.s.	7.5±2.2	n.s.	7.7±1.5	n.s.
	8 (3–10)	7 (2–10)		8 (3–10)		8 (4–10)	
Rey Auditory Verbal Learning Test Delay	47.1±14.6	47.0±13.8	n.s.	52.0±11.8	0.02	52.5±12.2	0.01

Outcome variables	Baseline (T1) (*n* =27)	Post control (T2) (*n* =27)	*P*-value (T1 *vs.* T2)	Post-HBOT (T3) (*n* =27)	*P*-value (T2 *vs.* T3)	2-mon follow-up (T4) (*n*=23)	*P*-value (T2 *vs.* T4)
Recall (T score)	47 (25–67)	50 (23–67)		53 (24–67)		57 (25–67)	
Post-Traumatic Stress Disorder Check	39.7±13.2	37.5±10.6	n.s.	27.0±9.6	< 0.0001	25.6±9.2	< 0.0001
List (total)§	37 (19–68)	36 (18–60)		22 (17–50)		22 (16–55)	

Note: Data are expressed as Mean ± SD, median (range), and are analyzed by paired samples *t*-tests. Scores are reported in standard scores, T-score format, or test manual scoring. Increasing scores indicate improvement except those marked with §. T1–4: Test points 1–4.

Two months after the last HBOT the two groups maintained or experienced further improvement on most of the outcome variables. Working memory, memory index, information processing speed, executive function, full scale IQ, HAM-D and -A, QOL, and PSQI showed continued improvement for the Treatment Group. The Control Group also maintained their gains but did not have as much improvement. Executive Function and sleep quality were the only two variables that showed a significantly greater improvement for the Treatment Group compared to the Control Group. In sum, both groups showed significant and equal improvement on nearly all outcome variables after treatment by the conclusion of the study.

The percentage that each of the PPCS Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV TR) definition symptoms improved or worsened for both groups during the 8-week HBOT and control period are shown in **Table 6**. Treatment Group subjects experienced significant improvement in all eight of the PPCS definition symptoms; however, easy fatigability, headache, vertigo/dizziness, irritability, and anxiety/depression were the most responsive symptoms to HBOT. The Control Group experienced worsening on six of eight symptoms during the control period.

Table 6

Percentage of DSM-IV TR persistent postconcussion syndrome definition symptoms in both groups that improved or worsened during the first 8-week study period

DSM-IV TR Persistent Postconcussion Syndrome definition symptoms	% Improve		P-value	% Worse		P-value
	Control Group	Treatment Group		Control Group	Treatment Group	
Fatigue	11	87	< 0.0001	*19*	*9*	< 0.000
Sleep	19	59	0.01	*4*	0	0.015
Headache	8	83	< 0.0001	*33*	0	< 0.000
Dizziness/vertigo	9	82	< 0.0001	*13*	0	< 0.000
Irritability	12	89	< 0.0001	*19*	0	< 0.000
Anxiety/depression	8	86	< 0.0001	*28*	0	< 0.000
Personality change	0	60	< 0.0001	0	0	–
Apathy	10	61	0.0009	0	0	–

Note: Improved symptoms in normal font, worsened symptoms in italics. n = 27 for Control Group and n = 23 for Treatment Group. DSM-IV TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

Both groups completed the HBOT treatment periods in near-identical times: 57.0 ± 5.02 days for the Control Group, 56.5 ± 5.00 days for the Treatment Group (P = 0.7144). The planned 2-month follow-up testing occurred in 79 days for the Treatment Group and 80 days for the Control Group, over 11 weeks for both groups. Eighty-seven percent of subjects were able to complete 40 HBOTs in 8 weeks and 96% were able to complete at least 30 HBOTs. There was no significant difference between Treatment Group (HBOT) and Control Group (control period) in the numbers in each group who experienced either an increase or decrease in psychoactive medication usage; however, a trend favored a reduction in the Treatment Group (P = 0.0785). Both groups reduced psychoactive medication usage by 30–41% during HBOT, but the difference between groups was insignificant (P = 0.4492). There was no difference between civilian and military subjects in PPCS and PTSD symptom reduction after HBOT (P = 0.2320 NSI, P = 0.3818 PCL).

Trajectory of weekly NSI scores during HBOT treatment for both groups and during the control period for Control Group are plotted in **Figure 4** (data in

Additional Table 1) along with corresponding trajectories of extracted Immediate Postconcussion Assessment and Cognitive Testing (ImPACT) symptom scores for the 240 kPa oxygen and 130 kPa air groups from Wolf et al.25 The trajectories for the Control Group and Treatment Group during HBOT are near identical, but different from the Wolf et al.25 groups and the Control Group in the control period. Comparison of ours and the Wolf et al.25 symptom scores to symptom scores in all other studies of HBOT in mTBI/PPCS are shown in **Table 7**.

Figure 4

Symptom trajectories of total persistent postconcussion syndrome symptom scores during and post-treatment or control.

Note: NSI: Neurobehavioral Symptom Inventory; ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing; COG: Control Group; TG: Treatment Group. ImPACT data were from Wolf et al.25

Additional Table 1

Total persistent postconcussion syndrome symptom scores this study and Wolf et al.25 during and post-treatment or control.

	NSI COG Control	NSI COG HBOT 150 kPa	NSI TG HBOT 150 kPa	ImPACT Control 130 kPa air	ImPACT HBO 240 kPa
Pre	44.6	42.1	39.0	~38.5	~37.0
Post week 1		35.0	29.3	~44.5	~37.5
Post week 2		32.7	25.1	~36.0	~33.0
Post week 3		28.1	21.6	~37.0	~33.0
Post week 4		27.1	22.2	~35.0	~34.0
Post week 5		24.2	21.9	~31.0	~34.0
Post week 6		24.3	20.5	~29.5	~35.5
Post week 7		20.6	17.9		
Post week 8		17.0	13.5		
Post hyperbaric oxygen therapy or control	42.1	16.5	12.7		
Six week follow-up				~26.0	~32.5
Two monthfollow-up		19.8	18.7		

Note: NSI: Neurobehavioral Symptom Inventory; ImPACT: Immediate Post-concussion Assessment and Cognitive Testing; COG: Control Group; TG: Treatment Group. ImPACT data was approximated and abstracted from Figure 2 in Wolf et al.25

Table 7

RPCS Q, ImPACT, and NSI symptom outcomes in civilian and military studies of hyperbaric oxygen therapy in the persistent postconcussion syndrome of mild traumatic brain injury according to dose of hyperbaric therapy

Study	Year	No chamber treatment	120 kPa air	130 kPa air	150 kPa O_2	200 kPa/21 kPa O_2	200 kPa/150 kPa O_2	200 kPa O_2	240 kPa O_2
Harch et al.24	2017				–36%*				
Wolf et al.25	2012			–32%ª					–12%
Cifu et al.27	2013					+1%*	+4%*	–12%*	
Miller et al.28	2014	–2%*	–35%*		–37%*				
		+3%ϕ	–21%ϕ		–11%ϕ				
Weaver et al.29	2018		+21%*		–2%*				
			+13%ϕ		–10%ϕ				
Harch et al. (present study)	–	–5.6%ϕ			–52%ϕ				

Note: Negative numbers are improvement and positive numbers are worsening of symptoms. '*' represents Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ); 'a' represents Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), and 'ϕ' represents Neurobehavioral Symptom Inventory (NSI).

Complications/side-effects

One Serious Adverse Event, a psychiatric deterioration/hospitalization which occurred 1 week after completion of HBOT was an annual Fall occurrence for a military subject that was deemed unrelated to HBOT. Two Unexpected Adverse Events/Unexpected Suspected Adverse Reactions occurred in two subjects who experienced fatigue with a reversal of improved symptoms late in the HBOT

protocol (39 and 34 HBOTs). This was attributed to oxidative stress/overdosing that resolved after 10 days and 4 weeks, respectively. All three events were reported to the Institutional Review Boards and U.S. Food and Drug Administration in Safety Reports. Mild reversible middle ear barotrauma during the prodrome of an upper respiratory infection occurred in one subject and perforation of a multiply previously perforated tympanic membrane (an expected and informed risk for this subject) in another subject during her first HBOT. She finished her HBOT course. Overall, there was an 8% (4/50 subjects) complication rate that was related to the HBOT.

DISCUSSION

This randomized clinical trial was undertaken to confirm22,24,26,28,29,39 or refute25,27 the efficacy of the 150 kPa oxygen dose of HBOT in mTBI PPCS. This study confirmed the efficacy of 150 kPa HBOT by demonstrating statistically and clinically significant, multi-domain improvements in patients with the PPCS of mTBI 4.6 years after their last TBI. This is the longest average delay to treatment of any of the mTBI/PPCS HBOT studies published.

Important findings in this study include significant improvements in postconcussion symptoms and seven other outcome variables [memory, cognition/speed of information processing (a computerized cognitive test battery, ANAM, developed and employed by the U.S. military for TBI), depression, anxiety, PTSD symptoms, sleep, and quality of life] in PPCS subjects treated with HBOT compared to a randomly assigned Control Group during the same period. The Control Group subsequently experienced the near identical and statistically indistinguishable improvements as the Treatment Group when they were crossed over and received HBOT. The improvement in PPCS symptoms (NSI) cannot be explained by test-retest improvements which have been shown to be minimal in a 30-day period or longer88 and less than the significant reliable change of eight points.88 Our subjects experienced a 26.3-point reduction in the NSI.

The NSI symptom improvement was mirrored in the improvements in DSM-IV TR PPCS definition54 symptoms. All eight DSM-IV TR PPCS symptoms were highly significantly improved in the Treatment Group compared to the Control Group while 13–38% of the Control Group demonstrated worsening of five of the eight symptoms during the control period. The only symptom that worsened for the Treatment Group was fatigue; 9% reported increased fatigue.

This may have been a sign of oxidative stress which appeared to be clinically significant in 4/50 subjects late in the protocol. This phenomenon was previously reported in a chronic brain injury HBOT study that employed higher doses or longer courses of HBOT89 and was possibly responsible for the "trend toward harm" in the 240 kPa oxygen group of Wolf et al.25 as reported by Scorza et al.90 The improvements in the NSI and DSM-IV TR PPCS definition symptoms are the dominant findings in this study. Since symptoms are the primary target of treatment in PPCS91 these findings have the greatest implications for patients with PPCS.

The results of the study are buttressed by multiple factors: 1) improvement in headache; 2) the use of a randomly assigned Control Group; 3) significant improvement in seven other outcome variables despite overall small sample size (n = 50) and smaller n of the Treatment Group compared to the Control Group (23 *vs.* 27); and 4) improvements post-HBOT with continued improvements in the nearly 3-month follow-up period that are generally contrary to the natural history of mTBI PPCS and uncharacteristic of placebo effects. The index inclusion criteria symptom for this study (headache) showed improvement in 83% of the Treatment Group, similar to 93% of military subjects with headache in another study on mTBI PPCS with PTSD.24 During the same period 33% of Control Group experienced worsening of headaches. This symptom has been identified as a primary symptom in TBI,57,58,59,91 the sole symptom distinguishing TBI/PPCS from PTSD,57 and is a surrogate marker for brain wounding in mTBI.10,92,93,94,95 The reduction in headache underscored that HBOT was treating TBI in this study and not just symptoms.91

The randomized controlled single-blinded design of the study was chosen to eliminate multiple causes of possible confounding and demonstrated that HBOT was responsible for the changes and improvements in symptoms, cognitive function, and emotional status as opposed to placebo effects or test-retest effects. This conclusion was supported by the data in Harch et al.23,24 where the magnitude of improvement was similar to our study, but the magnitude of those improvements was criticized because of the presence of PTSD and the lack of a treatment control.96 The present study excluded clinical PTSD, had a far lower PCL score (38.9 *vs.* 63.4 in Harch et al.24) and a treatment Control Group, yet the HBOT group in our study still showed significant cognitive and affective improvements compared to the Control Group. The conclusions of our study are further supported by the significant

functional imaging findings in both Harch et al.23,24 (military subjects) and Boussi-Gross et al.26 (civilian subjects) which were associated with significant improvement in symptoms, cognition, and emotional status similar to our study. Both studies demonstrated global improvements in brain blood flow and the Harch et al.24 study showed a normalization of pattern of blood flow that "could not be explained by placebo effects."23,24

Significant improvements occurred in the Treatment Group in the other seven outcome variables, including Memory Index and ANAM, compared to Control Group during the control period despite overall small sample size of the study (50 subjects) and disproportionately smaller sample size for the Treatment Group (23 vs. 27). In addition, the Treatment Group experienced non-significant increases in working memory, information processing speed, executive function, and Full Scale Intelligence Quotient (FSIQ) compared to the Control Group. The inability to achieve statistical significance for these 5 cognitive domains may be due to ineffectiveness of HBOT in these domains, test-retest effects, small sample size of the study and disproportionate smaller sample size in the Treatment Group than the Control Group, and the effects of 1.6 years of additional education in the Control Group on these cognitive domains.

The post-HBOT improvements in 11 and 13 outcomes seen in the Treatment Group and Control Group immediately after HBOT and continued improvements in memory, working memory, FSIQ, and processing speed in the nearly 3 months after HBOT (a possible tail-effect) are contrary to the natural history of mTBI PPCS, suggesting a cause and effect relationship of HBOT on improvement of PPCS deficits. The Treatment Group showed 58%, 76%, and 20% change score increases in Memory Index, FSIQ, and processing speed in the nearly 3-month follow-up period while the Control Group demonstrated 41%, 46%, and 37% increases, respectively. The natural history of PPCS as documented by the Veterans Administration,7 Defense and Veterans Brain Injury Center,97 and a civilian study6 showed a continued requirement for care or persistence of TBI symptoms for 4 years, 1 year, and 3 years, respectively. Post-HBOT further cognitive and affective improvements were demonstrated for symptoms in Harch et al.24 6 months after HBOT and in Wolf et al.25 6 weeks after treatment. They were not demonstrated in Weaver et al.29 for either symptoms or cognition where the 150 kPa HBOT group gains compared to the purported sham group were diminished by 3 months follow-up. The Weaver et al.29 results may be explained by the 70% of subjects with high risk

for sleep apnea98; cumulative effects of untreated sleep apnea may have eroded the improvements seen with HBOT in 3 months following HBOT. In addition, negative effects of testing at altitude in Colorado Springs (> 6000 feet, < 81 kPa) post-receiving HBOT at sealevel in two of three sites may have had a deleterious effect on performance similar to what was demonstrated in asymptomatic college students with remote mTBI with loss of consciousness99 and an animal model of HBOT in chronic mTBI.21 Pending medical boarding or disability status/compensation may have also influenced Weaver et al.'s29 results. The tail-effects observed in our study, Harch et al.24 and Wolf et al.25 are consistent with and possibly explained by HBOT's gene expression100,101,102,103,104 trophic changes105,106,107,108,109,110,111 that appear to be progressive.

The cognitive data reinforced a finding in Harch et al.,24 where subjects stated that they were abnormal/different from their premorbid level of function, yet most of their scores at time of randomization were in the normal range. After HBOT patients expressed that they felt more back to normal as in Harch et al.,24 were symptomatically and cognitively improved, and their scores were statistically and clinically improved. This indicated that they in fact were not at their "normal" level of function after their TBI even though their scores were in the "normal" range on standardized testing. Working memory was 96.3 and 104 pre-HBOT in Harch et al.24 and in this study and improved to 107.6 (+11.3 points) in Harch et al.24 and 113.7 (+10.2 points-Treatment Group) and 118.6 (+14 points-Control Group) in this study after HBOT. These "normal" WM scores suggest that reliance on a statistical deficit in memory compared to normals for the DSM-IV TR definition of PPCS may be insensitive when diagnosing PPCS. The common assumptions that mTBI does not affect IQ and that a "normal" FSIQ excludes mTBI cognitive deficits96,112,113 appear to be erroneous as well. In both Harch et al.24 and this study the pre-HBOT FSIQs were normal (98 in Harch et al.24 and 106 herein) and yet the subjects had mTBI and cognitive deficits. After HBOT the FSIQ improved 14.2 points in Harch et al.24 and 11.6 (Treatment Group) and 13.4 points (Control Group) in the current study, nearly a standard deviation.

Multiple researchers11,12,24,42,43,44,45,46 have pointed out that the differences in data and conclusions of all of the mTBI PPCS HBOT studies22,23,24,25,26,27,28,29,39,114,115 are best explained by different effects/outcomes of different doses of hyperoxia and/or hydrostatic pressure, including the most recent study by Weaver et al.29 The cluster of U.S.

Department of Defense-sponsored studies characterized different doses of hyperbaric therapy as sham controls. The sham groups, according to the definition of sham51 and the known bioactivity of hydrostatic pressure,50 were actually alternate doses of hyperbaric therapy.11,12,24 The mischaracterization of the low-pressure air doses as sham is supported by the headache data and the symptom trajectories during HBOT. Wolf et al.25 reported a significant ($P = 0.002$) 41% reduction in mean headache score on the ImPACT with the 130 kPa hyperbaric air group, but a non-significant 21% reduction in the 240 kPa oxygen group, while Cifu et al.27 reported no significant reduction in headache (Item 3) on the Rivermead post-concussion symptoms questionnaire with three different doses of HBOT and Harch et al.24 noted a 93% reduction and an 88% decrease in the current study. The other U.S. Department of Defense studies28,29 did not report headache. The trajectory symptom data in **Figure 4** shows different symptom trajectories for the NSI for the 150 kPa oxygen and Control Groups in the current study and the ImPACT 240 kPa oxygen and 130 kPa air doses in Wolf et al.25 All three trajectories are typical drug treatment response patterns that are distinctly different from placebo effect patterns identified in pharmaceutical studies.116 More importantly, the 240 kPa oxygen dose suggests a drug toxicity effect24 (improvement then loss of improvement with continued treatment) that was consistent with a "trend toward harm"90 in the isolated mTBI 240 kPa oxygen-treated group in Wolf et al.25 The differences in headache reduction and symptom trajectories in these studies suggest the differing effects of different doses of HBOT on PPCS11,12,24,26,42,43 and are inconsistent with placebo25,27,114,115 or ritual effects28 which would have demonstrated similar effects across all studies.

The finding from all of the HBOT-treated mTBI/PPCS studies is that two doses of hyperbaric therapy have shown benefit (150 kPa oxygen and 130 kPa air), three doses have shown no benefit (200 kPa pressure with three different doses of oxygen), one dose has shown equivocal results (120 kPa air), and one dose (240 kPa oxygen) is potentially harmful.90 Consistent with U.S. Food And Drug Administration Investigational New Drug evaluations this cluster of studies represents a dose-response evaluation of the dual components of HBOT, pressure and hyperoxia, in mTBI PPCS. The consistent finding is that all studies on HBOT in mTBI PPCS,22,24,26,28,29 including the current study, that have used the 150 kPa oxygen dose first pioneered in acute severe TBI,117 used in chronic TBI,19,20,30,31,32,33,34,35,36,37,38 and confirmed in an animal model of chronic mild TBI,21 have shown statistically significant

improvement in subjects. It is apparent that 40 treatments of 150 kPa oxygen for 60 minutes in an eight to ten-week period is a beneficial, valid, and durable treatment for mTBI PPCS. In addition, given the evidence for brain wounding in mTBI PPCS,10,92,93,95 HBOT's known effects on wound-healing14 and reparative/trophic effects in chronic animal mTBI21 and human mTBI PPCS,24,26,111 HBOT may be the first disease-modifying therapy91 for mTBI PPCS.

Limitations of the study

The crossover design is a minor limitation in that it precluded characterization of a post-control longitudinal comparison to the Treatment Group. Since the natural history of mTBI PPCS is well known to be permanent after a period of time, however, no spontaneous improvement post-control period would be expected. The absence of a non-crossover 2-month Control Group follow-up period does not weaken the conclusions of the study. A second limitation was lack of blinding of subjects to allocation. This was unavoidable since no true pressure control group methodology has been identified in hyperbaric therapy; however, the potential placebo effects of chamber experience and "ritual" have been seriously questioned.24 A third limitation is non-blinding of subjects to the principal investigator, the frequent interaction with the principal investigator during HBOT, and the non-blinded administration of the NSI by the hyperbaric technician at the treatment site. These factors likely contributed to the substantial treatment effect demonstrated for the NSI, but it does not explain the significant improvements in the other outcome instruments compared to the Control Group which were administered by the blinded neuropsychologist. A final limitation was the number of dropouts which necessitated increasing the sample size of the study.

Conclusions

A course of 40 daily, 5 days/week, 150 kPa 60-minute HBOT treatments delivered to civilian and military subjects with the persistent postconcussion syndrome of mild TBI an average of 4.6 years after last TBI resulted in significant improvements in postconcussion symptoms, cognitive variables (memory, cognition/speed of information processing), and behavioral/emotional problems (anxiety, depression, PTSD symptoms, sleep, and quality of life) compared to a randomly assigned Control Group. These improvements were duplicated in the Control Group after crossing over to

HBOT. In both groups most of the improvements were sustained and even improved for some tests nearly 3 months after the last HBOT, suggesting HBOT as a disease-modifying therapy for mTBI PPCS.

Additional files

Additional file 1: Full details of the Methods and Protocol.

Additional file 2: Construction of categorical variables to measure cognitive function.

Additional Table 1: Total persistent postconcussion syndrome symptom scores this study and Wolf et al.25 during and post-treatment or control.

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Footnotes

Conflicts of interest

Dr. Harch owns a small consulting company called Harch Hyperbarics, Inc. He also has a financial arrangement with the treatment facility which is the primary location of his medical practice. Part of the manuscript was presented at Hyperbaric Medicine International: HBOT 2019, The 13th Annual Hyperbaric Medicine Symposium in Charleston, SC, USA.

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Institutional review board statement

The study protocol was approved by the Institutional Review Boards of the United States Army Medical Research and Materiel Command Office of Research Protections Human Research Protection Office and the Louisiana State University School of Medicine (approval No. 7381) and registered on ClinicalTrials.gov (NCT02089594) on March 18, 2014.

Informed consent statement

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients or their legal guardians have given their consent for patients images and other clinical information to be reported in the journal. The patients or their legal guardians understand that their names and initials will not be published.

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Datasets analyzed during the current study are available from the corresponding author on reasonable request.

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