Hyperbaric Oxygen Therapy for Veterans With Treatment-resistant PTSD: A Longitudinal Follow-up Study

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ABSTRACT

Introduction:

PTSD is common among veteran combatants. PTSD is characterized by brain changes, for which available treatments have shown limited effect. In a short-term study, we showed that hyperbaric oxygen therapy (HBOT) induced neuroplasticity and improved clinical symptoms of veterans with treatment-resistant PTSD. Here, we evaluated the long-term clinical symptoms of the participants of that study.

Materials and Methods:

Veterans from our short-term study were recruited 1 or more years after completing HBOT. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and self-reported questionnaires were administered at a single site visit. Changes in clinical scores between long-term, short-term, and pretreatment evaluations were analyzed.

Results:

Of the 28 participants who received HBOT during or following the short-term study, 22 agreed to participate in the current study. At a mean of 704 ± 230 days after completing the HBOT course, the mean CAPS-5 score (26.6 ± 14.4) was significantly better (lower) than at the pre-HBOT evaluation (47.5 ± 13.1, $P < .001$) and not statistically different from the short-term evaluation (28.6 ± 16.7, $P = .745$). However, for the CAPS-5 subcategory D (cognition and mood symptoms), the mean score was significantly better (lower) at long-term than at short-term evaluation (7.6 ± 5.1 vs. 10.0 ± 6.0, $P < .001$). At the long-term compared to the pretreatment evaluation, higher proportions of the participants were living with life partners (10 (46%) vs. 17 (77%), $P = .011$) and were working (9 (41%) vs. 16 (73%), $P = .033$). Decreases were observed between pretreatment and the long-term follow-up, in the number of benzodiazepine users (from 10 (46%) to 4 (18%), $P = .07$) and in the median (range) cannabis daily dose (from 40.0 g (0-50) to 22.5 g (0-30), $P = .046$).

Conclusions:

The beneficial clinical effects of HBOT are persistent and were not attenuated at long-term follow-up of about 2 years after completion of HBOT. Additional long-term effects of the treatment were observed in social function and in decreased medication use.

INTRODUCTION

A recent review, published in *Military Medicine*, called for consideration of hyperbaric oxygen therapy (HBOT) for the treatment of veterans with treatment-resistant PTSD.[1] Since the publication of that review, the findings of our randomized controlled trial on the effect of a 60-session HBOT protocol on treatment-resistant PTSD were published.[2] The study included Israeli veteran combatants who failed to improve after psychotherapy and/or pharmacotherapy. Following HBOT, the mean Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (CAPS-5) score was significantly improved. In addition to the clinical improvement, improved brain activity and microstructural integrity were demonstrated, mainly in the fronto-limbic circuit, which is characteristically involved in PTSD pathogenesis.

Guideline-based treatments for PTSD include pharmacotherapies and psychotherapies;[3–5] yet their effects are limited and usually do not last after they are terminated.[6] Currently available HBOT protocols target PTSD by a different strategy, which aims to induce biological neuroplasticity.[7–23] Hyperbaric oxygen therapy includes inhalation of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA), thus enhancing the amount of oxygen dissolved in body tissues.[24] The combined action of hyperoxia and hyperbaric pressure triggers both oxygen- and pressure-sensitive genes, resulting in induction of regenerative processes, including stem cell proliferation and mobilization, angiogenesis, and mitochondrial proliferation and migration, together with improved tissue oxygenation.[7–23] A number of clinical studies demonstrated a neurotherapeutic effect of HBOT in various types of brain injuries such as poststroke, traumatic brain injury, and prolonged post-concussion syndrome, even years after the acute brain insult.[25–27] A few studies have also demonstrated

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significant clinical improvement in PTSD symptoms induced by HBOT.[28–34] However, most of these studies did not evaluate long-term treatment outcomes.

The current study is a long-term follow-up of our randomized controlled trial, which demonstrated promising short-term improvement induced by HBOT, among veterans with treatment-resistant PTSD.[2] Here, we evaluated the long-term clinical benefit of HBOT at least 1-year posttreatment.

METHODS

Study Design

We conducted a prospective, long-term follow-up study of a previously published study that evaluated short-term treatment outcome.[2] The initial study included male veterans with treatment-resistant PTSD lasting at least 4 years before study enrollment. Men were included in the original study if they had at least one trauma-focused therapy course and pharmacotherapy and fulfilled the CAPS-5 questionnaire diagnostic criteria for PTSD. The participants were randomly assigned 1:1 to HBOT and control groups. The treatment group attended 60 daily sessions, 5 days a week in a multiplace chamber (HAUX-Life-Support GmbH). Each session consisted of 90 min of exposure to 100% oxygen at 2 ATA, with 5-min air break every 20 min.[2] Upon completion of the study protocol, the participants in the control group were offered a 60-session HBOT course, similar to that of the treatment group.

Of 35 male veterans randomized to HBOT and control arms in the original study, 29 completed the study protocol: 14 in the active treatment arm and 15 in the control group. All the participants in the control arm were treated with HBOT after completion of the study protocol. However, one participant from the control group withdrew from HBOT treatment after five sessions. Thus, 28 participants of the original study were offered to participate in the current long-term follow-up study. The protocol was approved by the Shamir Institutional Review Board (111/20).

Participants were recruited at least 1 year after completion of the HBOT protocol, by a phone call at which a single study visit was scheduled. At the visit, the participants filled informed consent form before their inclusion in the study. The CAPS-5 questionnaire was filled on site, and the self-reported questionnaires (the Brief Symptom Inventory-18 (BSI-18)

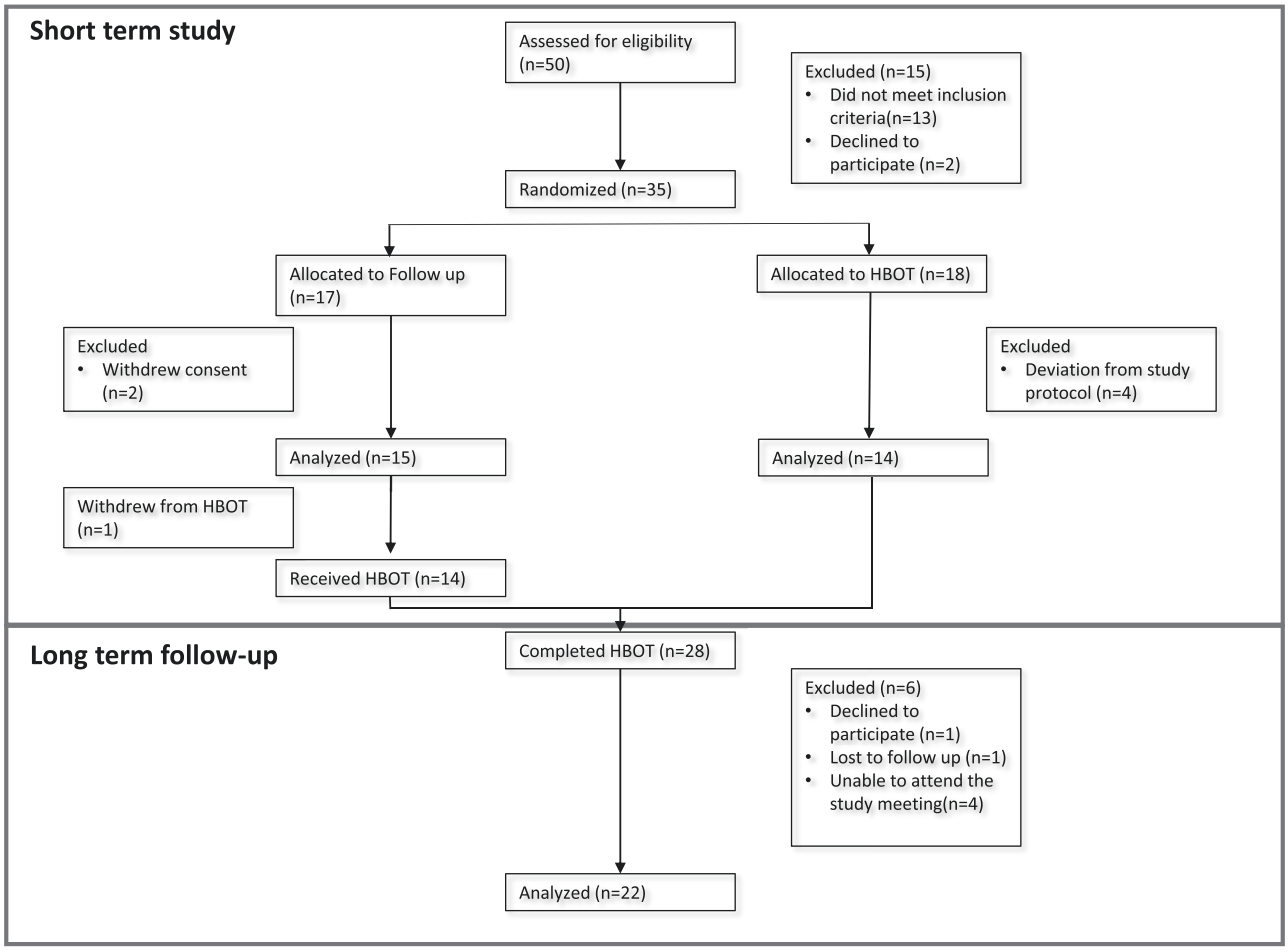

FIGURE 1. Study flowchart.

and the Beck Depression Inventory II (BDI-II)) were sent via email after the visit. Due to coronavirus disease 2019 restrictions, video calls replaced the site visits for some of the study participants.

Study Outcomes

The primary objective was CAPS-5 scores. The BSI-18 and the BDI-II questionnaires served as secondary clinical endpoints.

CAPS-5

Clinician-Administered PTSD Scale for DSM-5 is a structured interview-based test that consists of 30 items. The items are rated on a 0-4 severity scale. Twenty of the items reflect the severity of DSM-5 PTSD symptoms and served as the primary endpoint. The score ranges between 0 and 80, with higher scores indicating more severe PTSD symptoms. Item 28 in the CAPS-5 was used to evaluate the change from the last evaluation. The range of relevant scores was 0 to 4, where 0 is asymptomatic, 1 reflects considerable improvement, 2 moderate improvement, 3 slight improvement, and 4 no improvement (5 indicates insufficient information in the questionnaire but was not relevant to the study population).

BDI-II

The BDI-II is a widely used psychometric test for measuring the severity of depression. It consists of 21 multiple-choice questions and a self-report inventory about how the participant felt in the previous week. Each response is scored on a scale of 0 to 3. The range of total scores is 0 to 63; higher scores indicate more severe depression symptoms.

BSI-18

The BSI-18 contains 18 items in three symptom scales: somatization (6 items), depression (6 items), and anxiety (6 items). Each item is rated on the same 0-4 scale that reflects symptom severity in the previous 7 days, and the sum of all the responses yields a global severity index. Scores range between 0 and 72; higher scores indicate worse symptoms.

Statistics

Data are expressed as means ± standard deviations for normally distributed data, medians and interquartile ranges (quartiles 1-3) for variables that did not follow a normal distribution, and frequencies for categorical variables. Pretreatment and outcome measures were compared by the Wilcoxon rank-sum test for continuous variables, while the chi-square test was used to compare categorical variables. *P* values of <.05 were considered significant.

All the statistical analyses were performed using SPSS software, version 27.0 (IBM SPSS, Chicago, IL, USA).

TABLE I. Characteristics of the Study Participants Before Initiated Hyperbaric Oxygen Treatment

N	22
Age (years)	37.3 ± 9.8
Military exposure (years)	3 (2-10.5)
Time from the last combat exposure (years)	9 (4-14.25)
Total CAPS score	47.4 ± 13.1
Mild PTSD (20-39) *n* (%)	5 (23)
Moderate PTSD (40-59) *n* (%)	14 (64)
Severe PTSD (60-79) *n* (%)	3 (13)
Education (years)	14.2 ± 2.2
Life partner *n* (%)	10 (46)
Working *n* (%)	9 (41)
History pharmacotherapy *n* (%)	20 (91)
History of psychotherapy *n* (%)	22 (100)
PE *n* (%)	5 (23)
EMDR *n* (%)	14 (64)
CBT *n* (%)	20 (91)
Current medications	
SSRI/SNRI *n* (%)	13 (59)
BDZ *n* (%)	10 (46)
Antipsychotic *n* (%)	5 (23)
Cannabis *n* (%)	15 (68)
Cannabis (g/month)	40 (0-50)

Continuous variables are expressed as mean ± SD or medians (interquartile ranges) for non-normally distributed data. Categorical variables are expressed as percentages.

Abbreviations: BDZ, benzodiazepines; CBT, cognitive–behavioral therapy; EMDR, eye movement desensitization and reprocessing therapy; PE, prolonged exposure; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

RESULTS

Of the 28 men who completed 60 HBOT sessions, six did not participate in the current study: four because of technical issues (the inability to arrive at the center during the pandemic or technical challenges with video talks), one was afraid that answering a questionnaire would worsen his condition, and one was lost to follow-up. Thus, 22 men were enrolled in the current study and completed the CAPS-5 questionnaire. Four of the 22 participants did not fill the self-reported questionnaire. Thus, this study reports the long-term symptom load of 22 men and the self-reported questionnaires of 18 (Fig. 1).

Pretreatment characteristics of the participants are summarized in Table I. The mean age at the initiation of HBOT was 37.3 ± 9.8 years, and the median time from the last combat exposure was 9 (4-14.25) years. The mean CAPS-5 score was 47.4 ± 13.1. The study's follow-up ranged from 502 to 1,221 days (mean = 704 ± 230) after completion of the HBOT treatment course.

The total scores of CAPS-5 and of the CAPS-5 subcategories B, C, and E were similar at short-term and long-term follow-up (Table II and Fig. 2). The overall mean CAPS-5 score at the long-term evaluation was not statistically different from the short-term post-HBOT evaluation (Table II and Fig. 2). The CAPS-5 subcategory D (cognition and mood symptoms) score was significantly improved at the long-term follow-up compared to the short-term follow-up. The total

TABLE II. Mean Total and Subcategory Clinician-Administered PTSD Scale for DSM-5 Scores, at Pretreatment, and at Short-term and Long-term Evaluations after the Completion of 60 Sessions of Hyperbaric Oxygen Therapy

	Pre-HBOT	Post-ST	Post-LT	*P* value (pre-HBOT vs. post-ST)	*P* value (post-ST vs. post-LT)	*P* value (pre-HBOT vs. post-LT)
B. Intrusion symptoms	12.2 ± 3.7	6.6 ± 4.6	7.9 ± 4.2	<.001	.095	<.001
C. Avoidance symptoms	4.6 ± 2.1	3.2 ± 2.4	2.7 ± 2.2	<.001	.264	<.001
D. Cognition and mood symptoms	16.7 ± 5.3	10.0 ± 6.0	7.6 ± 5.1	<.001	.01	<.001
E. Arousal and reactivity symptoms	13.8 ± 4.6	9.5 ± 5.4	8.4 ± 4.6	<.001	.399	<.001
T. Total	47.5 ± 13.1	28.6 ± 16.7	26.6 ± 14.4	<.001	.475	<.001

Continuous variables are expressed as means ± SD and as medians (interquartile ranges).
HBOT, hyperbaric oxygen treatment; LT, long-term; ST, short-term.
P for group comparison by the Wilcoxon rank-sum test.

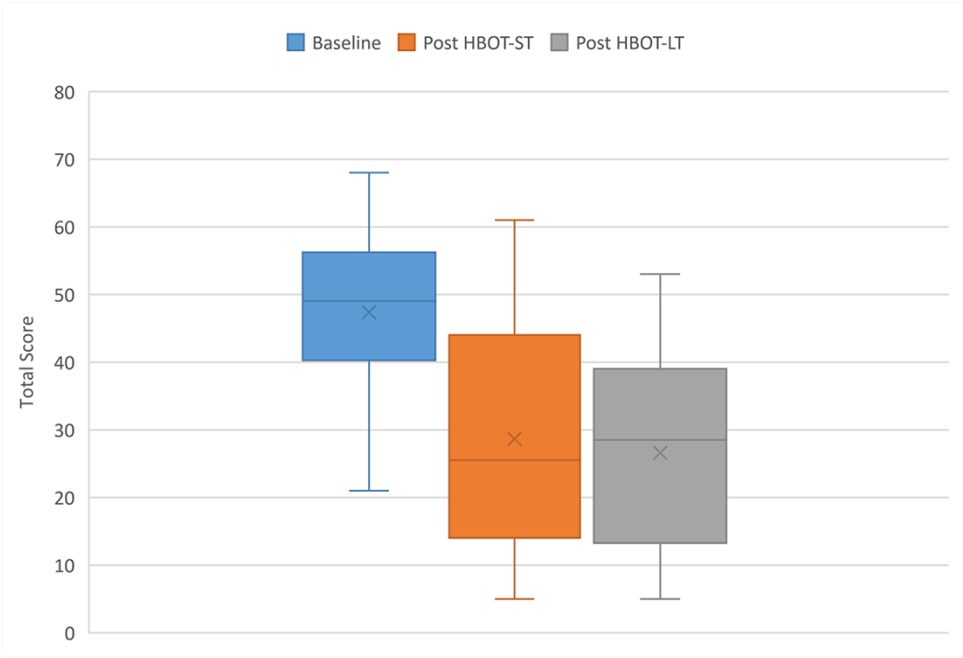

FIGURE 2. Clinician-Administered PTSD Scale score.

CAPS-5 score and all the subcategory scores were significantly improved at the long-term follow-up compared to pre-HBOT values.

At the long-term follow-up visit, the perceived overall improvement since the previous rating (the short-term post-HBOT evaluation), as assessed by item 28 in the CAPS-5 questionnaire, was reported as considerable by 3 participants, moderate by 8, and slight by 6. Five participants reported that no further improvement was noticed since study completion. None of the participants had higher (worse) CAPS-5 scores at the long-term follow-up visit than at the pre-HBOT visit.

Treatment response rates, defined as the proportion of patients with a 30% reduction in symptom scores compared to pre-HBOT, were 64% (14/22) at the short-term post-HBOT visit and 73% (16/22) at the long-term post-HBOT follow-up visit.

At the pre-HBOT evaluation, 10 (46%) participants had life partners and 9 (41%) were employed. At the long-term post-HBOT visit, these numbers were significantly higher: 17 (77%) and 16 (73%), respectively ($P = .011$ and $P = .033$, respectively).

At the long-term compared to pre-HBOT assessment, a significantly lower proportion of the participants was using benzodiazepines: 4 (18%) vs. 10 (46%), $P = .07$, and the overall cannabis dose was lower: 22.5 g (0-30) vs. 40.0 g (0-50), $P = .046$. The proportions of patients using selective serotonin reuptake inhibitors, antipsychotic drugs, and cannabis did not change between the pre-HBOT and long-term assessments.

No further improvement was observed in BSI-18 and the BDI-II scores at long-term post-HBOT compared to scores at the end of treatment (Table SI in the supplementary).

DISCUSSION

This study showed that in veterans with treatment-resistant PTSD, symptom improvement induced by HBOT was sustained. Clinical improvement in symptoms persisted during a follow-up period that lasted a mean 704 ± 230 days after completion of the HBOT protocol. The improvements mostly occurred during the course of HBOT. However, an additional significant improvement in mood and cognitive function was demonstrated at the long-term follow-up, beyond the improvement observed at the short-term follow-up. Improvements in cognition and mood may reflect a change in the way people perceive the world, as safety and self-esteem can only be rebuilt after improvement in PTSD core symptoms. Long-term improvement was also supported by subjective improvement, as assessed by item 28 in the CAPS-5 questionnaire; most participants felt that further improvement in symptoms occurred since the short-term assessment.

Clinical improvement was also accompanied by improved social and occupational performance. This is evident from the significant increase in the proportion of patients who were living with a life partner and of those who were employed at the time of the long-term follow-up. Furthermore, the participants significantly decreased their use of benzodiazepines and their dosages of cannabis.

As detailed in our short-term evaluation study that included functional and structural neuroimaging, the beneficial biological effect of HBOT is related to neuroplasticity effects, including brain activity and microstructural integrity in the relevant brain regions.[2] As such, HBOT represents a new therapeutic approach, different from pharmacotherapy, which obligates permanent administration, and from intensive psychotherapy, whose effects do not persist after treatment cessation.[35–38] Once the neurotherapeutic effect was induced by HBOT, a new steady state was achieved and the clinical improvement was persistent, long after HBOT cessation.

The current study is the first to evaluate the long-term effect of HBOT on veterans with military-related PTSD. Other clinical studies that evaluated the effect of HBOT on PTSD included persons with post-concussion syndrome as the primary inclusion criterion.[28–34] Two of those studies reported 6-12 months' follow-up evaluation, with conflicting results.[31,34] The discrepant results could be related to the differences in the study populations, the co-occurrence of traumatic brain injury, and the difference in HBOT protocols (pressure, in ATA, of the oxygen, and the number of sessions).[39]

A fundamental difference between psychotherapy and HBOT relates to the administration of the treatment. Psychotherapy is highly dependent on the operator's skills and the relationship established with the patient. These may explain a major difference between the results of some clinical studies and those of real life. On the other hand, HBOT uses a strict protocol, which enables objective evaluation of quality assurance, and which can be scaled up and followed by multiple centers across the globe. The role of the therapist is supportive and thus requires only simple training.

This study is limited by the lack of a long-term control group. This is because all the participants of the original study, including the control group, eventually received HBOT treatment.

At 2 years after completion of the study's HBOT protocol, a placebo effect related to participating in a study is expected to be minimal.

Theoretically, spontaneous recovery at 2 years, rather than preservation of HBOT's effect, could explain the favorable CAPS scores. However, the natural history of PTSD is chronic, and spontaneous remission is not expected after the first few months following the traumatic event.[40]

In conclusion, the beneficial effects of HBOT in veterans with treatment-resistant PTSD persisted and were not attenuated even 2 years after completion of the HBOT course. Furthermore, the beneficial effect of HBOT was even more pronounced in the long term, as reflected by additional improved social function and decreases in medication use.

ACKNOWLEDGMENTS

None declared.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

FUNDING

None declared.

CONFLICT OF INTEREST STATEMENT

S.E. is a shareholder and Chairman of the Medical Advisory Board in AVIV scientific.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author.

CLINICAL TRIAL REGISTRATION

Not applicable.

INSTITUTIONAL REVIEW BOARD

This study was approved by center's Institutional Review Board (ASF-111-20).

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

Not applicable.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

K.D.B. designed the study and drafted the original manuscript. I.K., E.L. and G.L. collected the data and reviewed the manuscript. I.B. analyzed the data. S.E. contributed to the study design and reviewed and edited the manuscript. All authors read and approved the final manuscript.

INSTITUTIONAL CLEARANCE

Institutional clearance was approved.

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