Hyperbaric Oxygen Therapy for Treatment-Resistant Posttraumatic Stress Disorder Without Traumatic Brain Injury: A Retrospective Cohort Study

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Abstract

Introduction: Hyperbaric oxygen therapy (HBOT) is a procedure used for indications such as wound healing due to its ability to promote neovascularization. For this reason, HBOT is being adapted for use in stroke, traumatic brain injury (TBI), and now in psychiatric disorders such as posttraumatic stress disorder (PTSD). The current study examines the possible efficacy of HBOT for improving PTSD-related symptoms without the context of TBI. *Methods*: Retrospective cohorts for PTSD patients without TBI were obtained through the TriNetX database. The treatment cohort had a history of HBOT and the control cohort did not have any HBOT. All PTSD patients had a history of both psychotherapy and pharmacotherapy to confer treatment resistance and PTSD severity. *Results*: The treatment group was associated with a significantly higher risk for sleep disorders (RR = 1.23 (95% *CI* (1.06, 1.43)), OR = 1.48 (95% *CI* (1.11, 1.97)), *P* = .007) and for depressive episodes (RR = 1.15 (95% *CI* (1.04, 1.27)), OR = 1.52 (95% *CI* (1.12, 2.06)), *P* = .007). No other outcome measured was significantly different between the two cohorts. *Discussion*: HBOT was not associated with improved PTSD-related symptoms in our study. Several factors may have led to these results such as lack of HBOT dosing data, long follow-up times, and lack of clinical symptom scales to confer disorder severity. *Conclusion*: Though the current study did not support current evidence that HBOT is an effective adjunct treatment for treatment-resistant PTSD, further studies are needed to better illustrate this relationship.

Keywords: posttraumatic stress disorder, hyperbaric oxygen therapy, depression, suicide, cognition, sleep disorder, substance abuse, alcohol abuse

Introduction

Hyperbaric oxygen therapy (HBOT) is the use of 100% oxygen at pressures greater than 1.4 atmosphere absolute (ATA) within an enclosed hyperbaric chamber monitored by a physician (Undersea and Hyperbaric Medical Society 2020). HBOT has been a widely used adjunct for wound healing due to its ability to promote neovascularization (Lam et al. 2017). Neovascularization is theorized to occur through two mechanisms: stimulation of angiogenesis by local endothelial cells and stimulation of vasculogenesis through recruitment of stem and progenitor cells (Thom 2011). This property has opened the door for HBOT to be adapted for neurological indications including stroke, traumatic brain injury (TBI), migraines, fibromyalgia, and, more recently, posttraumatic stress disorder (PTSD) (Doenyas-Barak et al. 2023, Leighton et al. 2024).

PTSD is a psychiatric disorder occurring after a potentially traumatic event. PTSD is characterized by re-experiencing of the event, hyperarousal, avoidance of triggers of the event, depression, and sleep disturbances such as nightmares. (American Psychiatry Association 2013).

The current gold standard therapy for PTSD includes psychotherapy and selective serotonergic reuptake inhibitors (SSRIs) (Schrader & Ross 2021). However, response rates to this treatment are only about 60% at most, with less than 20-30% of PTSD patients reaching full remission (Berger et al. 2009). HBOT may fill in this gap in patients with treatment-resistant PTSD. Though PTSD is a clinical diagnosis, biological changes in gray matter volume and neural activity are observed in functional magnetic resonance imaging (fMRI) and single-photon emission computerized tomography (SPECT) studies (Kunimatsu et al. 2020). In patients with PTSD, these changes are noted in areas related to fear, memory, emotional regulation, and executive functions such as the hippocampus, amygdala, and prefrontal cortex (PFC). fMRI studies indicate that HBOT may reverse these brain microstructure changes seen in PTSD by improving blood flow to such areas including the prefrontal cortex (PFC), hippocampus, and insula (Doenyas-Barak et al. 2022; Lin et al. 2019).

There have been numerous but conflicting investigations on the efficacy of HBOT for PTSD and TBI, especially in military cohorts (Biggs et al. 2022, Eve et al. 2016, Marcinkowska et al. 2021, Parr et al. 2021, Peterson et al. 2018). While some trials found significant improvement in many aspects of PTSD symptoms such as cognition and mood, several others have found no significant difference in outcomes with HBOT versus sham therapy (Biggs et al. 2022, Eve et al. 2016, Marcinkowska et al. 2021, Parr et al. 2021, Peterson et al. 2018). However, the majority of literature on this topic has focused on PTSD concurring with TBI and/or post-concussion syndrome (Harch et al. 2012, Harch et al. 2017). Some studies have also evaluated HBOT for PTSD in the context of fibromyalgia, a chronic pain disorder thought to be closely associated with psychological trauma (Boussi-Gross et al. 2024, Hadanny et al. 2018). Few recent investigations have isolated the efficacy of HBOT in patients with PTSD and without TBI. Two studies evaluated HBOT in veterans with PTSD related to military combat 1 to 4 weeks post-treatment and 1 year post-treatment, respectively, and found that while all symptoms of PTSD improved immediately after treatment when compared to pre-treatment scores, cognition, memory, and mood scores continued to uptrend in the long-term (Doenyas-Barak et al. 2022, Doenyas-Barak et al. 2022).

Indeed, many reports suggest that HBOT leads to improvement in PTSD-related mood symptoms such as depression and suicidal ideation (Doenyas-Barak et al. 2024, Harch et al. 2017, Shytle et al. 2019). HBOT has also been observed to improve depression as a sequela of stroke, especially when used as an adjunct with first-line antidepressants (Liang et al. 2020). This relationship may be mediated by HBOT attenuating neuroinflammation (Lim et al. 2017).

Though these results show promise for HBOT as an adjunct therapy for PTSD, current available studies are limited by small sample sizes, focus on military personnel only, inconsistent dosage of HBOT, and possible confounding of TBI. The current retrospective cohort study seeks to

investigate the possible efficacy of HBOT in mood symptoms in a cohort of PTSD patients using the TriNetX database.

Methods

We utilized a retrospective cohort design to investigate the value of HBOT for PTSD patients without TBI in a previously un-studied database. We gathered a sample of patients diagnosed with PTSD and created two cohorts: one with a history of HBOT and another with no history of HBOT through the TriNetX database. TriNetX is a global health research network providing researchers access to extensive deidentified patient information extracted from the electronic health records (EHRs) of over 250 million patients worldwide. These records are sourced from more than 220 healthcare organizations (HCOs), categorized into subnetworks based on region, capabilities, and data sources. Our study focused on a network of 61 HCOs, encompassing over 105 million patients exclusively from the United States in order to improve internal validity and application of findings in the U.S. healthcare system.

We consecutively sampled patients between the ages of 18 and 90 years and records reported from 2005 to 2025. We identified our two cohorts using inclusion and exclusion criteria from the International Classification of Diseases, 10th Revision (ICD-10) codes, Healthcare Common Procedure Coding System (HCPCS), Systematized Nomenclature of Medicine (SNOMED) codes, Current Procedural Terminology (CPT) codes, and Anatomic Therapeutic Chemical (ATC) codes. All patients included ICD-10-CM F43.1 Post-traumatic stress disorder (PTSD). In order to isolate patients with more severe and/or treatment-resistant PTSD, all patients also met both of the following criteria: CPT 1021137 Psychotherapy Services and Procedures; ATC N06AB Selective serotonin reuptake inhibitors. All patients were excluded if they met criteria for ICD-10-CM S06 Intracranial injury, traumatic brain injury. Finally, the treatment group (HBOT) met at least one of the following criteria: HCPCS G0277 Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval; HCPCS C1300 Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval (deprecated 2014); SNOWMED 18678000 Hyperbaric oxygen therapy; ICD-10-PCS 5A05121 Extracorporeal hyperbaric oxygenation, intermittent; ICD-10-PCS 5A05221 Extracorporeal hyperbaric oxygenation, continuous. The control group (no HBOT) were excluded if they met any of these criteria. We employed propensity-based balancing using the pre-specified covariates of age, sex, history of depressive episodes, history of MDD, and history of substance use disorders in order to address baseline differences between the cohorts.

Using the TriNetX analytics software, we compared the two cohorts on several outcomes related to PTSD mood symptoms after the index event. As this retrospective study was observational in nature, our analysis evaluated associations between HBOT and PTSD-related disorders. The index event was defined as the first day where all inclusion criteria were met for a patient.

Outcome 1 was “Depressive episode,” which was defined by ICD-10-CM F32 Depressive episode. Outcome 2 was “Major depressive disorder,” which was defined by ICD-10-CM F33 Major depressive disorder, recurrent. Outcome 3 (“Suicide attempt/Self-harm”) was met with one of the following criteria: ICD-10-CM T14.91 Suicide attempt; ICD-10-CM X71-X83 Intentional self-harm; ICD-10-CM F48 Other nonpsychotic mental disorders (*First known suicide attempt*). Outcome 4 or “Suicidal ideations” was met with ICD-10-CM R45.851 Suicidal ideations. Outcome 5 or “Sleep disorders” was met with ICD-10-CM G47 Sleep disorders. Finally, Outcome 5 or “Substance use disorders” was met with one of the following criteria: ICD-10-CM F10.1 Alcohol abuse; ICD-10-CM F19.1 Other psychoactive substance abuse. The “Measures of Association” analytic tool was used to evaluate each outcome by providing risk ratio, risk difference, and odds ratios for each outcome with respect to the two cohorts. The risk difference analysis included a T-test and an α value of .05 was used as the threshold for significance. Follow-up time was also calculated for the number of days between index event and the outcome measured.

Given the use of de-identified patient records and the absence of any collection, use, or transmission of individually identifiable data in this retrospective cohort study, it was deemed exempt from institutional review board approval and informed consent as per the Health Insurance Portability and Accountability Act (HIPAA). Furthermore, we strictly adhered to the reporting guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) framework throughout all phases of our investigation.

Results

Table 1. Demographics before and after balancing cohorts.

		Before Matching					*After Matching*				
		Mean	SD	Patients	% of Cohort	*P*-value	Mean	SD	Patients	% of Cohort	*P*-value
Age (years)	Treatment	53.6	14.1	382	100	<.001	53.6	14.1	382	100	.99
	Control	42.2	16.2	158,520	100		53.7	14.1	382	100	
Female	Treatment	-	-	265	69.37	.02			265	69.37	.88
	Control	-	-	118,503	74.76				267	69.90	
Male	Treatment	-	-	117	30.63	.01			117	30.63	.88
	Control	-	-	39,881	25.16				115	30.11	
Unknown Gender	Treatment	-	-	0	0	.57			0	0	-
	Control	-	-	136	0.09				0	0	

Table 2. Diagnostics before and after balancing cohorts.

		Before Matching			*After Matching*		
	Group	Patients	% of Cohort	*P*-value	Patients	% of Cohort	*P*-value
Depressive episode	Treatment	333	87.13	<.001	333	87.13	.83

Major Depressive Disorder	Control	115,073	72.59	.004	335	87.70	.94
	Treatment	229	59.95		229	59.95	
Sleep disorders	Control	83,457	52.65	<.001	230	60.21	1.00
	Treatment	235	61.52		235	61.52	
Alcohol abuse	Control	61,322	38.68	<.001	235	61.52	.87
	Treatment	104	27.23		104	27.23	
Other psychoactive substance abuse	Control	21,212	13.38	.55	102	26.70	1.00
	Treatment	33	8.64		33	8.64	
	Control	12,391	7.82		33	8.64	

Table 3. Follow-up data after balancing cohorts.

	Patients	*Mean Follow-up (Days)*	*SD*	*Median Follow-up (Days)*	*Interquartile Range*
Treatment	382	2220.44	1560.32	2019	2347
Control	382	1426.83	1426.83	1163	1679

Table 4. Measures of association for each outcome. *Statistically significant *P*<.05.

Outcome	*Cohort*	*Patients in Cohort*	*Patients with Outcome*	*Risk (%)*	*Risk difference (%) (95% CI)*	*z-score*	*P-value*	*Risk Ratio (95% CI)*	*Odds Ratio (95% CI)*
Depressive episode	Treatment	382	275	71.99	9.16 (2.55, 15.78)	2.702	.007*	1.15 (1.04, 1.27)	1.52 (1.12, 2.06)
	Control	382	240	62.83					
Major Depressive Disorder	Treatment	382	222	58.12	5.24 (-1.80, 12.27)	1.456	.15	1.10 (0.97, 1.25)	1.24 (0.93, 1.65)
	Control	382	202	52.88					
Suicide attempt/ Self-harm	Treatment	382	22	5.76	0.26 (-3.01, 3.53)	0.157	.88	1.05 (0.59, 1.87)	1.05 (0.57, 1.94)
	Control	382	21	5.50					
Suicidal ideation	Treatment	382	55	14.40	-3.40 (-8.61, 1.80)	-1.280	.20	0.81 (0.58, 1.12)	0.78 (0.53, 1.15)
	Control	382	68	17.80					
Sleep disorders	Treatment	382	199	52.09	9.69 (2.64, 16.73)	2.681	.007*	1.23 (1.06, 1.43)	1.48 (1.11, 1.97)
	Control	382	162	42.41					
Substance use disorders	Treatment	382	74	19.37	-3.93 (-9.73, 1.88)	-1.325	.19	0.83 (0.63, 1.09)	0.79 (0.56, 1.12)
	Control	382	89	23.30					

Our criteria output 158,520 patients in the control group and 382 patients in the treatment group. The cohorts were then balanced to have similar age, gender, and diagnostic distributions. The demographic results after balancing are shown in Table 1. After balancing, there were 382 patients in the treatment group and 382 patients in the control group. Age in the treatment group was *M*=53.6 years, *SD*=14.1 and in the control group was *M*=53.7 years, *SD*=14.1. Females made up 69.37% of the treatment group and 69.90% of the control group, and males made up the

other 30.63% and 30.11%, respectively. Cohorts were also balanced for past medical histories of depressive episodes, MDD, sleep disorders, alcohol abuse, and other psychoactive substance abuse. The proportions of these disorders in each cohort before and after balancing are displayed in Table 2. It is important to note that depressive episodes ($P < .001$), MDD ($P = .004$), sleep disorders ($P < .001$), and alcohol abuse ($P < .001$) before the index event were all significantly greater in the treatment group prior to balancing. After balancing the cohorts, the number of days to follow-up in the treatment group (M=2220.44, SD=1560.32) were higher than the control group (M=1426.83, SD=1426.03) (Table 3).

Measures of association, including risk difference, risk ratio, and odds ratio, were calculated for each of the diagnostic outcomes between the cohorts (Table 4). Depressive episodes were significantly higher in the treatment group than in the control group, RR = 1.15 (95% *CI* (1.04, 1.27)), OR = 1.52 (95% *CI* (1.12, 2.06)), $P = .007$. The risk of sleep disorders was also significantly higher in the treatment group compared to the control group, RR = 1.23 (95% *CI* (1.06, 1.43)), OR = 1.48 (95% *CI* (1.11, 1.97)), $P = .007$. The risks of MDD (RR = 1.10 (95% *CI* (0.97, 1.25)), OR = 1.24 (95% *CI* (0.93, 1.65)), $P = .15$), suicide attempt/self-harm (RR = 1.05 (95% *CI* (0.59, 1.87)), OR = 1.05 (95% *CI* (0.57, 1.94)), $P = .88$), suicidal ideation (RR = 0.81 (95% *CI* (0.58, 1.12)), OR = 0.78 (95% *CI* (0.53, 1.15)), $P = .20$), and substance use disorders (RR = 0.83 (95% *CI* (0.63, 1.09)), OR = 0.79 (95% *CI* (0.56, 1.12)), $P = .19$) were not statistically significant between the two cohorts.

Discussion

The present study sought to investigate the possible efficacy of HBOT in improving PTSD symptoms in a large cohort of patients without TBI. The results did not support an associated improvement in depressive episodes, MDD, suicidal ideation, suicide attempts, sleep disorders, or substance use disorders in the treatment group when compared to the control group. Unexpectedly, the risks of depressive episodes and sleep disorders at follow-up were significantly higher in the treatment group than in the control group. Given the relative novelty of this treatment for PTSD without concurrent TBI, the variables influencing these results are likely complex.

There were several factors in this analysis to be considered when interpreting the results. The greatest limitation in the methodology is the lack of dosage or indication information available for HBOT. Dosage of the HBOT can be influenced by pressure, duration of each session, and number of sessions (Andrew & Harch 2024). The effect of HBOT on PTSD symptoms has been shown to be dose-dependent (Andrew & Harch 2024). Higher doses of HBOT were associated with a transient symptom exacerbation characterized by increased emotional volatility that spontaneously improved with continued treatment. In the current study, follow-up times vary and whether or not symptoms of depression are recorded as a result of initial high doses of HBOT

cannot be confirmed. In addition to a dose-dependent relationship between HBOT dosage and PTSD symptom severity, there appears to be a threshold dose required for PTSD symptom improvement to persist long-term (Danan et al. 2025). In this 2025 randomized controlled trial comparing HBOT to sham treatment, patients with ≥35% improvement in PTSD symptoms directly after treatment had sustained improvements at 3-months follow-up. Doenyas-Barak et al. (2022) also showed improvements in symptoms 1-year post-treatment with similar dosage of HBOT (60 total 90-minute sessions at 2 ATA). Our average follow-up time for the treatment group was about 6 years, and thus we cannot guarantee with the existing literature that symptom improvement due to HBOT would have persisted to follow-up. Further, longer average follow-up times in the treatment group may also lead to greater chance of exhibiting at least one depressive episode and/or sleep disturbance.

We also acknowledge that by balancing the cohorts for gender, age, and common comorbidities, the size of the cohorts were greatly reduced and impacted the power of our analysis. Reduced sample size of the balanced cohorts also limited the number of potential confounding variables that could be controlled. Future investigations should consider exploring the effect of additional variables such as psychiatric and other medications, previous PTSD treatment trials, and other indications of wound healing to measure response to HBOT.

A further limitation of the current study is the lack of clinical symptom scales supported by the TriNetX database. The mainstay measures of PTSD and related symptoms in existing literature are clinical scales such as the clinician-administered PTSD scale-V (CAPS-V) and Beck's Depression Inventory (BDI) (Doenyas-Barak et al. 2022, 2024). Such scales are more sensitive for changes in symptom severity than only using those who meet full diagnostic criteria as an outcome. Leighton et al. (2024) point out that in many studies of HBOT in PTSD, improvement in symptom severity found using these clinical scales did not necessarily correlate with remission of the disorder. In fact, many participants that showed statistically significant improvements in PTSD and depression symptoms through these scales still met diagnostic criteria for PTSD (Harch et al. 2017). It is possible that the severity of related disorders such as MDD and substance use improved despite patients still meeting diagnostic criteria for each disorder.

The significant increase in depressive episodes seen in the treatment group may be explained by the association between depression and delayed wound healing. One of the most common current uses for HBOT is for chronic wounds that are persistent or recurrent to healing (Thackham et al. 2008). Though we cannot verify the indication for HBOT given in our dataset, we can glean from this data that the majority of patients underwent HBOT for wound-healing purposes. Depression is strongly associated with longer-persisting wounds and wounds associated with greater pain, such as those that may require HBOT (Zhou & Jia 2016). Further, one review found that depression can slow the rate of wound healing and affect the size of the wound over time (O'Donovan et al. 2025). Though our study cohorts were balanced for previous depressive

episodes, those requiring HBOT for wound healing may have had higher risk for future depressive episodes for these reasons. Closely related to this relationship is the connection between chronic wounds and sleep disturbance. Wounds that are resistant to healing over time and those associated with pain are more likely to cause stress and sleep disturbance (Fauziyah & Gayatri 2018). More severe wounds requiring HBOT may explain the significant increase in sleep disorders seen in our treatment group.

These results contribute to the already contradictory evidence that HBOT improves PTSD symptoms. The majority of studies have examined PTSD in the context of TBI, relied on small sample sizes, and used inconsistent paradigms of HBOT (Biggs et al. 2022, Peterson et al. 2018). Focus on PTSD may pave the way for HBOT to be used as an adjunct in other psychiatric disorders. Studies of HBOT for stroke recovery have promising results for improvement of depression symptoms, revealing possible utility for MDD (Liang et al. 2020). Other reviews found scant evidence for HBOT on autism and schizophrenia, but the efficacy of HBOT in primary psychiatric disorders is largely unexplored (Raphaeli et al. 2019). Our study explored the possible efficacy of HBOT for PTSD without TBI and in a larger sample than those previously recorded. Our results show that there is still more to be explored for the role ofHBOT in psychiatry.

Conclusion

The current study sought to examine the associations between HBOT and PTSD severity in a population with treatment-resistant PTSD and no TBI across several healthcare organizations in the United States. The results of the study showed higher risks of depressive episodes and sleep disorders in the treatment group, while all other outcomes were not statistically significant between groups. These results further muddy the waters of the already inconclusive literature on this topic. There were a number of limitations to our current study that may have influenced these results, and we believe that further investigations are needed to control for dosage and frequency of HBOT, PTSD symptom severity, and follow-up times. This study contributes to the currently limited body of research on HBOT for PTSD unrelated to TBI, and future work should isolate this population to explore expanded use of HBOT in psychiatric disorders.

Competing Interests: Authors have declared that no competing interests exist.

Author Contributions: Lily Charron designed the study, conducted a literature search, performed the statistical analysis, and wrote the initial manuscript draft. Eduardo Espiridion supervised all aspects of the project. All authors read and approved the final manuscript.

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