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Original Article

Hyperbaric Oxygen Therapy for the Management of Mild and Moderate Traumatic Brain Injury: A Single-Center Experience

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Background

Hyperbaric oxygen therapy (HBOT) has been shown to be an effective modality in the management of a variety of conditions. However, its role in the treatment of traumatic brain injury (TBI) remains an area of controversy. This study aims to evaluate the safety and outcomes of HBOT in managing the long-term sequelae of TBI.

Methods

The records of TBI patients who underwent increments of 40 sessions of HBOT at 1.5 atmosphere absolute at a single medical center were reviewed. The outcome measures included physical, cognitive (i.e., Trail Making Test, parts A and B; U.S. Department of Veterans

Affairs' Evaluation of Cognitive Impairment and Subjective Symptoms tool), and single-photon emission computed tomography findings. The complications and withdrawals were recorded.

Results

During the study period, 17 patients underwent HBOT to manage the long-term sequelae of their TBI. Of the 17 patients, 12 (70.6%) completed 120 HBOT sessions and were evaluated 3 months after treatment. All 12 patients had statistically significant improvements in their Trail Making Test, parts A and B, and U.S. Department of Veterans Affairs' Evaluation of Cognitive Impairment and Subjective Symptoms scores ($P < 0.05$). Additionally, single-photon emission computed tomography depicted increased cerebral blood flow and oxygen metabolism among studied subjects compared with the baseline values. A total of 5 patients withdrew from the study, which was related to new-onset headaches associated with HBOT for 1 patient.

Conclusions

HBOT using 1.5 atmosphere absolute in increments of 40 sessions was found to be a safe and effective modality in the management of the long-term sequelae of TBI. HBOT should be considered in the management of this patient population.

Previous Next

Key words

Cerebral blood flow; Hyperbaric oxygen therapy; Outcomes; Persistent postconcussion syndrome; SPECT; Traumatic brain injury

Abbreviations and Acronyms

ATA, Atmospheric absolute; FDA, Food and Drug Administration; GCS, Glasgow coma scale; HBOT, Hyperbaric oxygen therapy; SPECT, Single-photon emission computed tomography; TBI, Traumatic brain injury; VAECI, U.S. Department of Veterans Affairs' Evaluation of Cognitive Impairment and Subjective Symptoms

Introduction

Despite the technological advances and management of patients with traumatic brain injury (TBI), TBI continues to be a significant cause of mortality and morbidity in the United States (U.S.).[1] It is estimated that 4.1 million TBIs occur annually, with ~80,000 people becoming disabled from TBIs in the U.S. each year and 5.3 million Americans requiring assistance with activities of daily living because of TBI.[2, 3, 4] Therefore, TBI and its consequences result in substantial public health and economic burdens on societies, with an estimated $76.5 billion annually spent on TBI management.[5,6] Ischemia has been implicated as a significant factor in the pathogenesis of TBI.[7] The lack of oxygenation causes a shift from aerobic to anaerobic metabolism, resulting in acidosis and depletion of cellular energy. A cascade of events eventually manifests itself in a myriad of symptoms attributed to TBI.[8]

Hyperbaric oxygen therapy (HBOT) is a novel method for managing poorly healed wounds, decompression sickness, and carbon monoxide poisoning, among others.[9] The high oxygen tension is believed to aid in healing by improving tissue oxygenation, angiogenesis, anti-inflammatory properties, and enhancing neuroplasticity.[10, 11, 12, 13, 14, 15] Various studies have delineated HBOT efficacy in in the management of mild and severe TBI.[16, 17, 18, 19] Although randomized clinical trials showed contradictory results regarding HBOT's role and efficacy in TBI, significant limitations remain regarding their methodologic designs and biases.[20] The use of HBOT for TBI is not a new concept; its use can be traced back to the 1960s, when it was first introduced to treat cerebral gas and/or air embolism.[21, 22, 23] The selection of hyperbaric pressure and the number of sessions used for TBI patients was based on early studies that reported success with a pressure of 1.5 atmosphere absolute (ATA) and 40 sessions, with few variations.[24,25]

In the present study, we aim to delineate the efficacy and safety of HBOT in managing the long-term sequelae of patients with TBI. We describe our protocol, report our clinical, cognitive, and radiologic outcomes, and add to the growing body of literature on this emerging topic.

Methods

Patient Population, Study Objectives, and Treatment Protocol

Using our institutional database, we retrospectively reviewed patients with TBI who underwent HBOT at Jupiter Medical Center between 2012 and 2019. The institutional review board approved the present study (approval no. 20180334), and all included patients provided written informed consent. Supplemental patient records and electronic medical records were reviewed to evaluate the patients' clinical history, imaging findings, and outcomes. Patients with isolated mild and moderate TBI (defined as a Glasgow coma scale [GCS] score of ≥13 and 9–12, respectively) with evidence of concussion and loss of consciousness and a minimum injury timing of 1 year before enrollment were included in the present study. The study exclusion criteria were age <18 years, pregnancy, untreated pneumothorax, receipt of antimetabolite chemotherapeutic agents, active infection, severe TBI (i.e., GCS score of <9), penetrating head

injury, and TBI as a part of polytrauma. A manual review of the medical records was performed to verify that the patients met the inclusion criteria and to obtain clinical variables.

The present study is a case series and does not have a control group. Additionally, because of the small number of participants and events, a multivariable analysis controlling for the confounding factors was not feasible. The primary objective of the present study was to evaluate the safety and efficacy of HBOT in managing the long-term sequelae of TBI. The secondary objectives were to assess the physical and cognitive outcomes of the patients, including the Trail Making Test, parts A and B, and the U.S. Department of Veterans Affairs' Evaluation of Cognitive Impairment and Subjective Symptoms (VAECI) tool, and single-photon emission computed tomography (SPECT) evaluations. We also recorded any complications and withdrawals associated with HBOT.

The following variables were collected from the electronic medical records of the patients: age, sex, GCS score, SPECT findings, cognitive assessment results, level of disability, and complications.

The management protocol and treatment session details were adopted in accordance with the previous literature.[24,25] Each patient had undergone a clinical evaluation and cognitive assessment before the first HBOT session, after 40, 80, and 120 sessions, and 3 months after treatment to document the patient's progress and response to treatment. SPECT was performed only at baseline and after 40 HBOT sessions. If the clinical evaluation, SPECT scan, and cognitive assessment demonstrated improvement after 40 sessions, another 40 HBOT sessions were administered. HBOT was discontinued after a 40-session interval if these domains did not show improvement. The patients also underwent cognitive and physical assessments 3 months after the final HBOT session. Patients could stop the sessions at any point during the study period.

HBOT Protocol

HBOT was performed using a SIGMA 3400 monoplace hyperbaric chamber (Perry Baromedical Corp, Palm Beach, Florida, USA). The chamber pressurization and depressurization control system is entirely pneumatic. An AMSE UV-stamped pressure relief valve protects the pressure vessel from accidental overpressurization. The chamber accommodates 1 individual at a time. The chamber was used to deliver 40 HBOT sessions during the course of 5 to 6 months with 5 sessions weekly. The session protocol included 60 minutes at a pressure of 1.5 ATA using 100% oxygen from liquid oxygen (Matheson Inc., Sharon Hill, Pennsylvania, USA). A total of 15 minutes was used for both compression and decompression at 1 m/min to reach a pressure of 1.5 ATA.

Cognitive Assessment

The cognitive assessment included the Trail Making Test, parts A and B.[26] Both parts consist of 25 circles distributed over a sheet of paper. The patient was asked to draw lines as quickly as possible to connect the numbers (part A) and both numbers and letters (part B) in ascending order. The time taken to complete the task was recorded and compared with the predetermined reference range.

The physician assessed the patient's level of disability at each interval. Additionally, the VAECI tool was used during the physician's evaluation as an objective measure of the patient's level of disability.[27] The physician evaluated ≤38 facets of cognitive impairment (e.g., memory, attention, judgment, motor activity, communication, visual–spatial orientation), with a score of 0–38. Lower scores are associated with better results and less disability.

Imaging Findings

SPECT is a known reliable method for measuring cerebral blood flow and metabolism and has been reported in numerous studies. A detailed description of the SPECT guidelines has been previously reported.[28,29] The SPECT results after 40 treatments were compared with the baseline findings to document improvement. Improvement in cerebral blood flow was defined as an increase in cerebral blood flow as depicted on SPECT scans after 40 HBOT sessions compared with baseline. A single independent, experienced neuroradiologist interpreted and analyzed the imaging findings.

Statistical Analysis

Statistical analysis was performed using Prism, version 9 (GraphPad, San Diego, California, USA). A paired *t* test was used, and *P* values of < 0.05 were necessary to be considered statistically significant. Continuous variables are reported as the mean±standard deviation, and percentages are reported for categorical variables.

Results

Patient Population

During the study period, a single-arm, case series of 18 patients with mild and moderate TBI were enrolled in the study without a control group. The present study included 12 men (66.7%) and 6 women (33.3%), with a mean age of 49.8 ± 15.9 years. The interval from TBI to beginning HBOT ranged from 1 to 32 years. One patient voluntarily withdrew early from the study after enrollment because of a diagnosis of Alzheimer's disease. The other 17 patients underwent baseline assessments and 40 HBOT sessions.

Cognitive Outcomes

The cognitive evaluation was performed using the Trail Making Test, parts A and B, and the VAECI tool. In the Trail Making Test, part A, the average baseline score for the 17 patients was 32 seconds. After 40 and 80 sessions, 14 patients (82.4%) had statistically significant improvements in their Trail Making Test, part A, score ($P < 0.001$), with a mean improvement of 5.3 and 5.0 seconds, respectively. After 120 HBOT sessions, 12 patients demonstrated improvement, with a mean improvement of 8.6 seconds ($P < 0.001$). At the 3-month follow-up visit after the last HBOT session, 10 patients had a mean improvement in their Trail Making Test, part A, score of 11.4 seconds compared with baseline ($P < 0.003$; Table 1 and Figure 1).

Table 1. Cognitive Outcomes Using Trail Making Test, Part A, After HBOT

Treatment	**Patients (*n*)**	**Patients with Improvement (*n*)**	**Mean Improvement Compared with Baseline**		***P* Value**
			Time (seconds)	**Percentage**	
After 40 sessions	17	14	−5.3	18.9	< 0.001
After 80 sessions	17	14	−5.0	16.1	< 0.001
After 120 sessions	13	12	−8.6	28.8	< 0.001
At 3 months after last session	12	10	−11.4	30.0	< 0.003

HBOT, hyperbaric oxygen therapy.

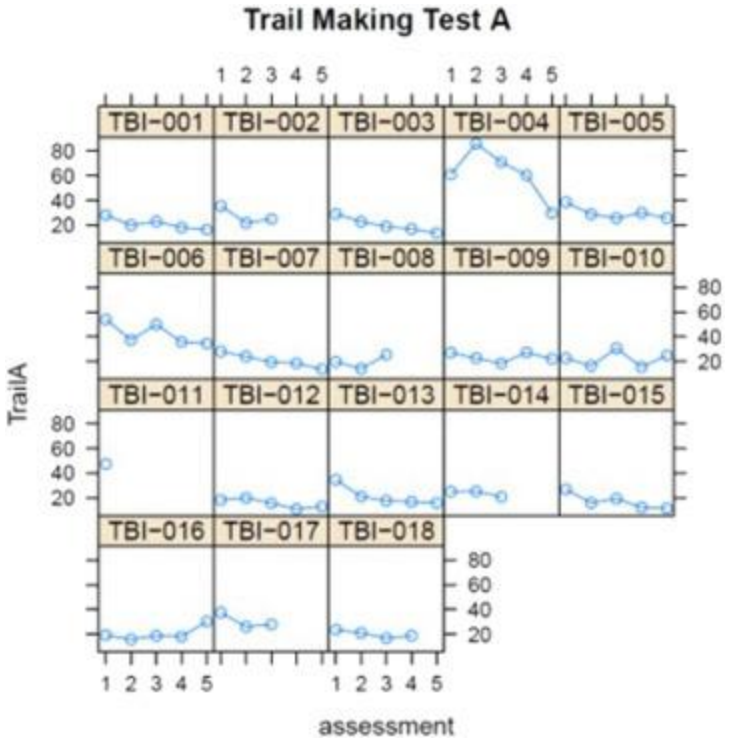

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Figure 1. Trail Making Test, part A, scores stratified by patient. Assessment 1 is at baseline, assessment 2 is after 40 sessions, assessment 3 is after 80 sessions, assessment 4 is after 120 sessions, and assessment 5 is at the 3-month follow-up after the last hyperbaric oxygen therapy session. TBI, traumatic brain injury.

In the Trail Making Test, part B, the average baseline score for the 17 patients was 95.8 seconds. A total of 13, 12, 11, and 12 patients had improvement in their Trail Making Test, part B, after 40, 80, 120 sessions and 3 months after the last HBOT session, respectively. The mean improvement after 40, 80, and 120 sessions and 3 months after the last HBOT session was 9.8, 9.7, 26.8, and 25.1 seconds, respectively ($P<0.05$; Table 2 and Figure 2).

Table 2. Cognitive Outcomes Using Trail Making Test, Part B, After HBOT

Treatment	Patients (*n*)	Patients with Improvement (*n*)	Mean Improvement Compared with Baseline		*P* Value
			Time (seconds)	Percentage	
After 40 sessions	17	13	−9.8	10	< 0.006
After 80 sessions	17	12	−9.7	10.8	< 0.025
After 120 sessions	13	11	−26.8	27.2	< 0.002
At 3 months after last session	12	12	−25.1	34.1	< 0.001

HBOT, hyperbaric oxygen therapy.

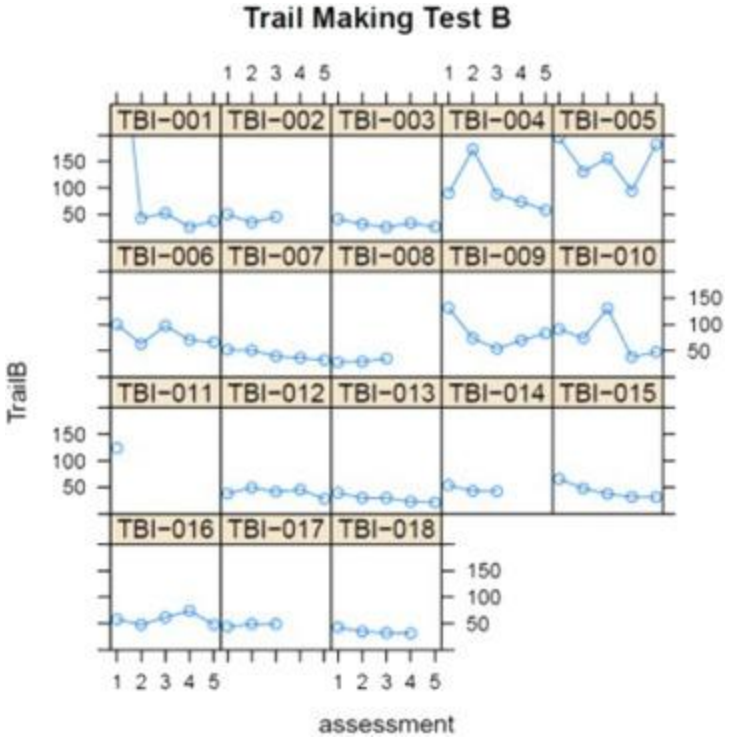

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Figure2. Trail Making Test, part B, scores stratified by patient. Assessment 1 is at baseline, assessment 2 is after 40 sessions, assessment 3 is after 80 sessions, assessment 4 is after 120 sessions, and assessment 5 is at the 3-month follow-up after the last hyperbaric oxygen

therapy session. The baseline observation for patient TBI-001 was 480 and is not shown on the plot. TBI, traumatic brain injury.

A total of 16 patients had VAECI assessments. The average baseline score was 12.2 (range, 5–20). After 40, 80, and 120 HBOT sessions and 3 months after the last HBOT session, 14, 16, 12, and 11, patients demonstrated improvement in the VAECI score, respectively. The mean improvement in their score at 40, 80, and 120 sessions and 3 months after the last HBOT session was 3.2, 5.9, 6.3, and 6.8, respectively ($P < 0.05$; Table3 and Figure3).

Table3. Cognitive Outcomes Using U.S. Department of Veterans Affairs' Evaluation of Cognitive Impairment and Subjective Symptoms Tool After HBOT

Treatment	**Patients (*n*)**	**Patients with Improvement (*n*)**	**Mean Improvement Compared with Baseline**		***P* Value**
			Score	**Percentage**	
After 40 sessions	16	14	−3.2	23.5	< 0.05
After 80 sessions	16	16	−5.9	43.4	< 0.05
After 120 sessions	12	12	−6.3	50.5	< 0.05
At 3 months after last session	11	11	−6.8	52.9	< 0.05

HBOT, hyperbaric oxygen therapy.

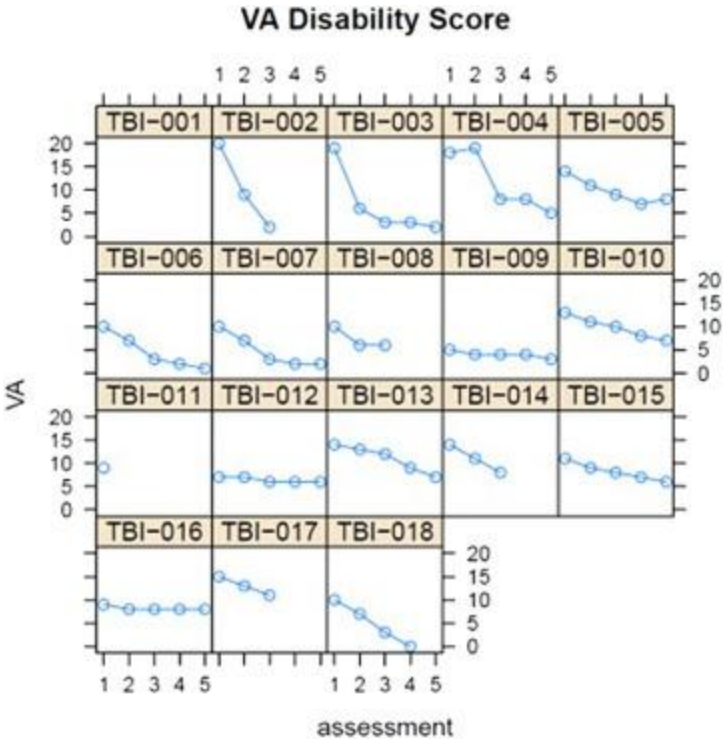

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Figure3. Veterans Affairs' (VA) Evaluation of Cognitive Impairment and Subjective Symptoms disability test scores stratified by patient. Assessment 1 is at baseline, assessment 2 is after 40 sessions, assessment 3 is after 80 sessions, assessment 4 is after 120 sessions, and assessment 5 is at the 3-month follow-up after the last hyperbaric oxygen therapy session. TBI, traumatic brain injury.

SPECT Outcomes

A total of 8 patients had SPECT scans at baseline and after 40 HBOT sessions. Among these patients, a significant increase was found in cerebral blood flow after 40 sessions of HBOT compared with that at baseline (Figure4).

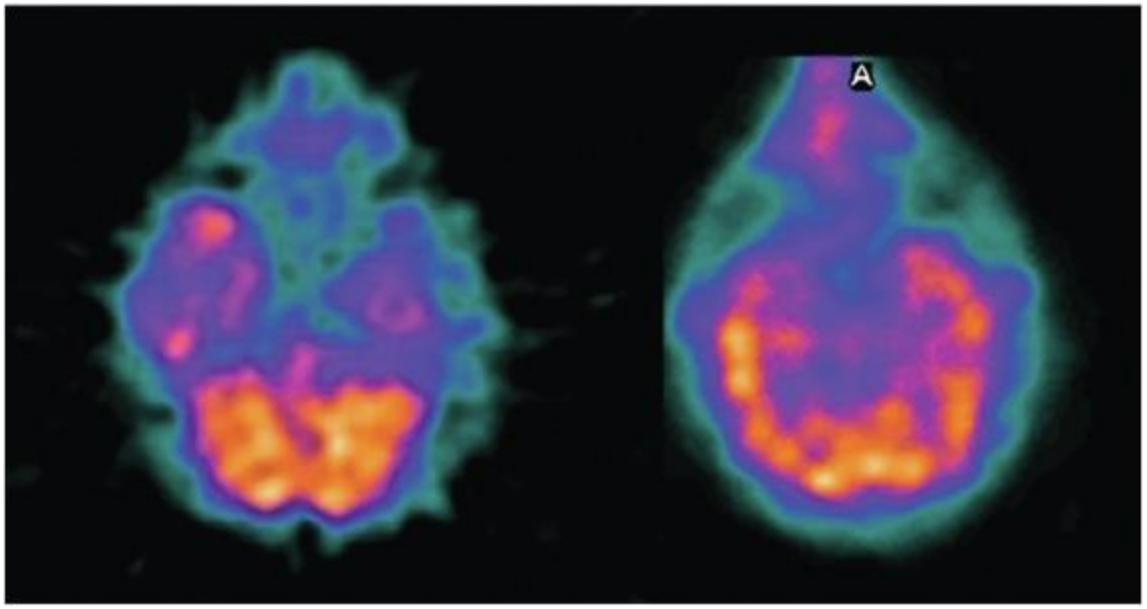

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Figure4. Single-photon emission computed tomography scan at baseline (Left) demonstrating an obvious lack of symmetry between the hemispheres. After 40 sessions of hyperbaric oxygen therapy, a significant increase could be seen in cerebral blood flow (Right).

Withdrawals and Complications

Five patients withdrew from the study. One patient withdrew immediately after enrollment and before beginning baseline testing because of a diagnosis of Alzheimer's disease. The other 4 patients withdrew from the study at different intervals (Figures1 and 2). One complication was encountered in patient 14, who withdrew from the study because of headaches associated with HBOT. The other 3 patients withdrew from the study for personal reasons.

Discussion

TBI is a prevalent condition with significant lifelong effects on patients, economies, and healthcare systems.[2,30,31] To date, no proven treatments are available to address the long-term cognitive, mental, emotional, and physical outcomes associated with TBI. Various modalities have been investigated and reported in the literature, each with inherent advantages and limitations. HBOT has been approved by the Food and Drug Administration for use in many conditions, including nonhealing wounds, decompression sickness, and

carbon monoxide poisoning, among others.[9] The applications of HBOT have expanded to include patients with musculoskeletal injuries, traumatic brain and spinal cord injury, and stroke, with promising results.[18,25,32, 33, 34] HBOT delivers pure oxygen at high pressure, which increases the amount of oxygen in the blood and tissues, correcting tissue hypoxia and chronic hypoxemia, and aid in healing and management of various pathological processes.[35] HBOT can be conducted using either a monoplace or multiplace chamber, and the duration of each session can vary between 1.5 to 2 hours, 1 to 3 times daily, with 20 to 60 therapeutic sessions depending on the condition.[24,25]

HBOT increases the production of reactive oxygen species, which improve neovascularization, enhance immunomodulatory properties, and exert its clinical efficacy. HBOT has been proposed as a promising approach for treating TBI owing to its ability to enhance oxygen delivery to the brain and promote tissue recovery and healing.[8] Studies have shown that HBOT can be effective in treating TBI at various levels of severity. For mild, moderate, and severe TBI, HBOT has been shown to improve cognitive function, reduce inflammation, enhance cerebral metabolism, improve blood flow, and reduce brain edema, resulting in decreased morbidity and mortality.[8,17,24,36, 37, 38] A systematic review on the use of HBOT for severe TBI found that HBOT led to improved Glasgow outcome scale scores in a specific subset of patients at 6 months after treatment.[8] Similarly, other studies noted improvements in social behavior, disability, and hospital stays among patients who underwent HBOT.[8] Additionally, some investigators found reduced mortality rates for patients who had received HBOT at 10 days after the injury and a higher chance of complete recovery.[8] Despite this, HBOT is considered a promising therapeutic approach for TBI patients, particularly for those who have not responded to traditional treatments or who have persistent symptoms.[10, 11, 12, 13, 14, 15,39] However, there has been colossal controversy regarding HBOT efficacy, with contradictory results reported in these randomized clinical trials.[25,40, 41, 42] Harch et al.[25] reported a randomized clinical trial comparing 25 patients with mild TBI who underwent 1.5 ATA HBOT for 40 sessions to 27 patients in the control group. They found statistically significant improvement (i.e., 26.3-point decrease) in the Neurobehavioral Symptom Inventory persistent postconcussion syndrome symptom score compared with a 2.5-point decrease in the control group ($P< 0.0001$).[25] Additionally, the treatment group had improved memory, cognition/speed of information processing, depression, anxiety, post-traumatic stress disorder symptoms, sleep, and quality of life compared with the control group. When the control group crossed over to the treatment arm, they experienced improvements almost identical to those in the HBOT group.[25]

However, other randomized clinical trials failed to show such a difference. Many investigators reported cardinal limitations in the design and conduct of some of these randomized clinical trials.[17,20,43] The sham group in multiple studies was a “pseudo-sham.” A number of these studies compared the treatment group to a sham group that had received some form of partially pressurized oxygen to prevent them from knowing their allocation but, thus, created a partial treatment group with therapeutic benefit. Second, significant heterogeneity is present in the treatment protocols, sample sizes, selection bias, ATA pressures, interval breaks, session lengths, and outcome measures, limiting accurate comparisons between groups. Third, many of these randomized clinical trials had stringent

inclusion and exclusion criteria, creating study populations not representative of those in the real world. Additionally, it is important to remember that the presence or absence of statistical significance does not necessarily correlate with clinical significance. A treatment could yield statistically significant results that are not clinically significant and vice versa. Finally, some investigators attributed the improvements following HBOT to placebo effects. Although such effects cannot be entirely excluded, the significant improvements across multiple domains, subjectively and objectively, cannot be entirely explained by a placebo effect alone.

HBOT has been found to be effective in managing the long-term sequelae of TBI in many case reports, observational studies, and randomized clinical trials (Table4). HBOT has been used in both civilian and military settings for both mild and severe TBI patients, with promising results. HBOT has been shown to reduce intracranial pressure and brain swelling, leading to faster recovery and symptom improvement. Harch et al.[18] reported their experience with 1.5 ATA HBOT among 30 military patients with mild TBI. The patients experienced statistically significant improvements in their self-reported symptoms and Rivermead Post-Concussion Symptom Questionnaire, reduced suicidal ideation and psychoactive medication use, and improved SPECT cerebral blood flow after HBOT. Similarly, Ma et al.[44] examined the effects of 20 sessions of 1.3 ATA HBOT among firefighters with mild TBI and mild emotional distress using magnetic resonance imaging. The study found increased limbic (i.e., hippocampus and parahippocampal regions) blood flow in the patients after the HBOT. Similar to these studies, our report of 17 adult patients who underwent HBOT after TBI showed improvements in physical, cognitive, and SPECT outcomes. Specifically, at least 70.6% of the patients benefited from the treatment and had significant improvement in the Trail Making Test and VAECI scores after 40, 80, 120 sessions and 3 months after HBOT. SPECT imaging also demonstrated increased cerebral blood flow and brain metabolism among the 8 patients after 40 sessions compared with baseline. These findings are in conjunction with the literature supporting HBOT use in TBI patients.

Table4. Examples of Reported Randomized Clinical Trials on HBOT for Traumatic Brain Injury

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT03900182 ↗; https://ClinicalTrials.gov/sho	The Role of Hyperbaric Oxygen and Neuropsychological	2.5	100	None	None	None	Wechsler Adult Intelligence scale-III; Cognitive Ability Screening	Hyperbaric oxygen	All	18–65	120

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
w/NCT03900182 ↗	Therapy in Cognitive Function Following Traumatic Brain Injury						Instrument; Mini-Mental State Examination; Short-Form 36-item questionnaire; World Health Organization Quality of Life questionnaire, brief version; Beck Depression Inventory				
NCT03339037 ↗; https://ClinicalTrials.gov/show/NCT03339037 ↗	Hyperbaric Oxygen Therapy Effect on Post Concussion Syndrome in Children	2.0	100	1.0	21	Perfusion; MRI+ DTI; PET-CT; SPECT	Cognitive function; post-concussion syndrome symptoms; Health Behavior inventory; balance; quality of life; brain network analysis; behavior; executive functions	Hyperbaric oxygen; no hyperbaric oxygen but normobaric air (sham); hyperbaric oxygen at 1.5 ATA, no normobaric hyperoxia	All	8–16	70

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT02407028 ↗; https://ClinicalTrials.gov/show/NCT02407028 ↗	Hyperbaric Oxygen Brain Injury Treatment Trial	1.5–2.5	100	1.0	Room air	None	Glasgow outcome scale, extended; duration of intracranial pressure elevation; therapeutic intensity level scores for controlling intracranial pressure; brain tissue partial pressure of oxygen; serious adverse events; peak brain tissue oxygen during HBO sessions	Hyperbaric oxygen at 2.0 ATA, no normobaric hyperoxia; hyperbaric oxygen at 2.5 ATA, no normobaric hyperoxia; hyperbaric oxygen at 1.5 ATA plus normobaric hyperoxia; hyperbaric oxygen at 2.0 ATA plus normobaric hyperoxia; hyperbaric	All	16–65	200

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
								oxygen at 2.5 ATA plus normobaric hyperoxia; normobaric hyperoxia; other: usual care			

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT02089594 ↗; https://ClinicalTrials.gov/show/NCT02089594 ↗	Hyperbaric Oxygen Treatment to Treat Mild Traumatic Brain Injury (mTBI)/Persistent	1.5	100	None	None	None	Neurobehavioral Symptom Inventory; Working Memory Index; Memory Index; Information	Hyperbaric oxygen; no hyperbaric oxygen	All	18–65	50

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
	Post-Concussion Syndrome (PPCS)						Processing Speed Index; Executive Function Index; Wechsler Adult Intelligence Scale, Full Scale Intelligence Quotient; Automated Neuropsychological Assessment Metrics; Hamilton Depression Scale; Hamilton Anxiety Scale; Quality of Life after Brain Injury; Pittsburgh Sleep Quality Index; Benton Visual Retention Test; Rey Auditory Verbal Learning Test Delay Recall; Post-Traumatic Anxiety Symptoms – Civilian Version				

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT01986205; https://ClinicalTrials.gov/show/NCT01986205 ↗	Hyperbaric Oxygen for Traumatic and Non-traumatic Brain Injury	1.5	100	1.0	Room air	None	Neurobehavioral symptoms; Inventory Incidence of Myopia	Hyperbaric oxygen; minimal pressure air	All	18–70	150
NCT01847755 ↗; https://ClinicalTrials.gov/show/NCT01847755 ↗	Hyperbaric Treatment of Traumatic Brain Injury (TBI)	1.5	100	None	None	SPECT	Improved cognitive function	Oxygen at 1.5 ATA	All	≥18	18

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT01611194 ↗; https://ClinicalTrials.gov/show/NCT01611194 ↗	mTBI Mechanisms of Action of HBO2 for Persistent Post-Concussive Symptoms	1.5	100	1.2	Room air	None	Presence of post-concussion symptoms after traumatic brain injury using the RPQ (RPQ-3 and RPQ13)	Hyperbaric oxygen at 1.5 atm; no hyperbaric oxygen (sham control at 1.2 atm)	All	18–65	71

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT01306968 ↗; https://ClinicalTrials.gov/show/NCT01306968 ↗	Hyperbaric Oxygen Therapy (HBO2) for Persistent Post-concussive Symptoms After Mild Traumatic Brain Injury (mTBI)	1.5	100	1.2	25	None	Post-intervention post-concussion symptom scores using the RPQ; change in post-concussion symptom scores using the RPQ	Hyperbaric oxygen; no hyperbaric oxygen (sham with hyperbaric air)	All	18–65	79

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT01220713 ↗; https://ClinicalTrials.gov/show/NCT01220713 ↗	Hyperbaric Oxygen Therapy (HBO2T) for Post-Concussive Symptoms (PSC) After Mild Traumatic Brain Injury (mTBI)	1.5 and 2.0	75 and 100	1	10.5	Neuroimaging	Improvement on symptom assessment battery; Neuropsychological Testing Battery; neurophysiologic measures of human performance (computerized dynamic posturography,	Procedure: hyperbaric oxygen therapy; treatment 1, 1.5 atm with 75% oxygen (balance of 25% nitrogen); treatment 2, 2.0 atm with 100% oxygen	All	19–60	60

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
							neuroimaging, eye tracking); common military task tests; neurophysiologic measures of human performance (computerized dynamic posturography, eye tracking)	(no nitrogen); no hyperbaric oxygen (sham control at 1 atm with 10.5% oxygen (balance of 89.5% nitrogen)			
NCT00810615 ↗; https://ClinicalTrials.gov/show/NCT00810615 ↗	Treatment of Traumatic Brain Injury With Hyperbaric Oxygen Therapy	2.4	100	1.3	Room air	fMRI	Computerized cognitive test scores (ImPACT Verbal Memory); Post-traumatic Stress Disorder Checklist – Military Version scores; Computerized cognitive test scores from ImPACT Visual Memory, ImPACT Processing Speed,	Hyperbaric oxygen at 2.4 ATA; no hyperbaric oxygen (sham treatment at 1.3 ATA)	All	19–60	50

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
							ImPACT Reaction Time, BrainCheckers Simple Reaction Time, BrainCheckers Code Substitution, BrainCheckers Procedural Reaction Time, BrainCheckers Go-NoGo Reaction Time, BrainCheckers Matching To Sample, and BrainCheckers Code Sub Recall				
NCT00760734; https://ClinicalTrials.gov/show/NCT00760734 ↗	Hyperbaric Oxygen Therapy (HBOT) in Chronic Traumatic Brain Injury (TBI)/Post Concussion Syndrome (PCS)	1.5	100	None	None	SPECT	Psychometric testing; quality of life measurements; return to school or work	Low-pressure hyperbaric oxygen therapy at 1.5 ATA	All	18–65	30

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
	and TBI/Post-Traumatic Stress Disorder (PTSD)										
NCT00715052 ↗; https://ClinicalTrials.gov/show/NCT00715052 ↗	The Effect of Hyperbaric Oxygen Therapy on Patients Suffering From Neurologic Deficiency Due Traumatic Brain Injury	1.5	100	None	None	SPECT	Neurologic evaluation	Hyperbaric oxygen therapy	All	≥16	60
NCT00170352 ↗; https://ClinicalTrials.gov/show/NCT00170352 ↗	Comparison Between Different Types of Oxygen Treatment Following Traumatic Brain Injury	1.5	100	None	None	None	Using sliding dichotomized Glasgow outcome scale score for 6 months	Combined HBO2 and normobaric hyperoxia (60 minutes of HBO2 at 1.5 ATA, followed by normobaric	All	16–65	80

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
								hyperoxia for 3 hours of 100% fraction of inspired oxygen at 1.0 ATA); control (standard care)			
NCT00830453; https://ClinicalTrials.gov/show/NCT00830453 ↗	Hyperbaric Oxygen Therapy in Chronic Stable Brain Injury	1.5	100	None	None	None	Neuropsychological measures; questionnaires; neurologic examination; physical functioning measures	Comply with protocol and tolerate 60 hyperbaric oxygen sessions; estimate immediate and long-term effects of hyperbaric oxygen therapy for those with chronic brain injury	All	18–80	60

NCT Number; URL	Title	Group				Imaging	Cognitive Tests	Interventions (Extended)	Gender	Age (years)	Enrol (*n*)
		Intervention		Control							
		Pressure (ATA)	Oxygen (%)	Pressure (ATA)	Oxygen (%)						
NCT03205215 ↗; https://ClinicalTrials.gov/show/NCT03205215 ↗	Hyperbaric Oxygen for Post Concussive Syndrome	2	100	None	None	None	Change in the RPQ; change in NIH Tool Box; change in 9-item Patient Health Questionnaire; change in Short-Form Health Survey; change in Quality of Life After Brain Injury; change in World Health Organization Disability Assessment Schedule, version 2.0	Hyperbaric oxygen therapy	All	19–65	150

ATA, atmosphere absolute; CT, positron emission tomography-computed tomography; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; HBO, hyperbaric oxygen; MRI, magnetic resonance imaging; NR, not reported; NIH, National Institutes of Health; PET- NA, not available/not applicable; RPQ, Rivermead Post-Concussion Symptom Questionnaire; RPQ-3, 3-item Rivermead Post-Concussion Symptom Questionnaire; RPQ-13, 13-item Rivermead Post-Concussion Symptom Questionnaire; SPECT, single-photon emission tomography; UCSD, University of California, San Diego.

Various ATA pressures have been reported in the literature, ranging from 1.15 to 2.4.[17] It is generally accepted that a pressure of 1.3–1.5 is associated with a noticeable benefit without increasing the risk of complications such as middle ear barotrauma, ocular disturbances, and oxygen toxicity associated with high ATA pressures.[17] When the pressures exceeds these values, concerns exist regarding the safety and oxygen toxicity risk. We used 1.5 ATA as our pressure setting in our series to avoid such complications. We have not encountered any serious adverse events related to HBOT, and only 1 patient developed headaches related to HBOT and withdrew from the study. Although HBOT is generally considered safe, it is not without risks and potential complications.[45] One of the most common side effects of HBOT is middle ear barotrauma, which occurs because of changes in the air pressure in the chamber and can cause ear pain, dizziness, and hearing loss.[45] Ocular disturbances, such as cataracts and retinal damage have also been reported in rare cases.[46] In addition, oxygen toxicity can occur with prolonged exposure to high levels of oxygen, resulting in seizures, respiratory distress, and other complications.[45] Although extremely rare, it is important to carefully monitor patients during HBOT sessions to detect and manage any potential complications.

Study Limitations

To interpret our results, it is important to consider the limitations of our study. First, the sample size was small, and no control group was included, limiting the generalizability of our findings. The study only included patients with mild and moderate TBI; thus, it is uncertain whether the results apply to patients with severe TBI. Additionally, the lack of a long-term follow-up period beyond 3 months after the final HBOT session hinders the assessment of sustained treatment effects. Therefore, it is difficult to draw definitive conclusions regarding the efficacy of HBOT in managing the long-term sequelae of TBI. Retrospective data collection was used, which can be subject to selection bias and missing data. Additionally, the evaluators conducting the VAECI cognitive assessment were not blinded, which could have resulted in an observer bias. However, we believe that the noticeable improvements across all measured domains cannot be attributed to observer bias alone and were actual benefits from HBOT. The emotional and psychological outcomes for TBI patients (e.g., postconcussion syndrome, sleep dysfunction, and post-traumatic stress disorder) were not measured. Finally, the present study did not analyze the specific anatomic areas of improved SPECT blood flow measurements nor capture other quantitative imaging findings such as those from positron emission tomography.

Conclusions

Our study provides promising results for the use of HBOT in managing the sequelae of mild and moderate TBI. The study found that HBOT was effective in improving physical, cognitive, and SPECT outcomes for the majority of patients who underwent HBOT, with significant improvements in the Trail Making Test and VAECI scores after HBOT. SPECT imaging also demonstrated increased cerebral

blood flow and brain metabolism among our patients after HBOT sessions compared with that at baseline. These findings support HBOT for TBI patients and highlight the importance of appropriate pressure settings to avoid complications and maximize outcomes.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Barry M. Miskin, Conception and design, study supervision, data collection, statistical analysis, critical revision, final approval. Lee A. Fox, Conception and design, data collection, statistical analysis, critical revision, final approval. Hussam Abou-Al-Shaar, Statistical analysis, writing – original draft, critical revision, final approval. Othman Bin-Alamer, Writing – original draft, critical revision, final approval. Aaron Goertz, Data collection, critical revision, final approval. Conner T. Lipin, Data collection, critical revision, final approval. Nicole Fertig, Data collection, critical revision, final approval. Nevada Cox, Data collection, critical revision, final approval.

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