Hyperbaric Oxygen Therapy for Traumatic Brain Injury in an Iraq War Veteran

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Footnotes: Related informed consent videos of interviews with this study participant as well as others who participated in the pilot study can be found at: http://www.ORCCAHBO.com. All patient identifiers have been removed from the case study and imaging results.

Disclosures: This patient provided informed consent to participate in a pilot study of hyperbaric oxygen treatment (HBOT) in addition to standard psychiatric care and physical therapy in servicemen with traumatic brain injury (TBI) conducted by Oxygen Rescue Care Centers of America. Care was provided on a *pro bono* basis and involved multiple providers. R.H.C. provided treatment and conducted the baseline and post-treatment assessments. Organizations that provided lodging, travel expenses, and meals for the study participants include the American Red Cross. GE provided Ceretec for brain single-photon emission computed tomography (SPECT) scans.

Summary

Physical injury to servicemen from improvised explosive devices (IEDs) is well-documented; however, exposure to IED detonation can cause nonvisible traumatic brain injury (TBI). This case study documents what occurred to one veteran diagnosed with PTSD after multiple blast exposures; he had attempted suicide and was receiving treatment with psychotropic medications. After 40 hyperbaric oxygen therapy treatments (HBOT) and comprehensive physical therapy, the comparison of pre- and post-treatment neuropsychological tests and single-emission photon computed tomography (SPECT) brain scans documented significant improvement in neurocognitive function, motor skills, mental health state and quality of life.

Introduction

The Defense and Veterans Brain Injury Center recently reported that many servicemen returning from Afghanistan and Iraq experienced a traumatic brain injury (TBI) during deployment.¹ One study found that of the 1.64 million troops deployed to Iraq or Afghanistan by 2008, as many as 300,000 were suffering from mild TBI/post-traumatic stress disorder (PTSD) or depression.² One study noted that 88% of military personnel treated at an echelon II medical unit in Iraq had been injured by an improvised explosive device (IED) or mortar, with 47% of injuries involving head trauma.³ Some of the resulting neuropsychological problems caused by blast exposure are now categorized as PTSD, the symptoms of which mimic those of TBI.⁴ An increase in suicide rates has also been reported among U.S. veterans.^{5,6}

Neurologic symptoms associated with TBI vary in severity, appear randomly, and may be triggered by events years after the initial injury.⁷ The damage caused by an IED cannot be minimized: in animal studies, isolated exposure of the torso even while the head was protected caused brain damage.⁸ TBI from explosive blasts can be caused by the barotrauma of the blast or through coup/contrecoup injuries,⁹ causing diffuse axonal damage in individual neural cells.⁹⁻¹¹ Barotrauma usually involves air-filled organs and tissue-density interfaces, and causes critical damage to organs such as the lungs and ears,^{10,12} as well as the brain parenchyma and vasculature.

Hyperbaric oxygen therapy (HBOT)—in which patients breathe 100% percent oxygen in a pressurized, closed environment—has been used to treat infections and chronic wounds, decompression illness, carbon monoxide poisoning, TBI, stroke, and a variety of neurological disorders associated with perfusion/metabolism abnormalities.^{13–15} The decreased mortality and improved clinical outcomes after HBOT in patients with TBI¹⁶ undoubtedly are related to the

physiological, biochemical, and pharmacological effects associated with HBOT. HBOT reduces edema and, by enhancing oxygen diffusion, it overcomes ischemia/hypoxia; stimulates cell metabolism and energy production (which alleviates local acidosis and reactivates idling neurons and probably also glial cells in the ischemic penumbra); promotes local perfusion, metabolism, and neovascularization; reduces cerebral arterial gas embolisms; and scavenges free radicals.^{13,14,17-19}

Based on these known effects of HBOT, we hypothesized that it may be useful in the treatment of IED-related TBI/PTSD, producing improvements in neurocognitive function, motor skills, and behavior that would allow dose reduction or elimination of psychotropic medications. The rationale of our approach is based on observations by Sukoff et al²⁰ that hyperbaric oxygen decreases cerebral edema by as much as 20%, as well as the idea that supersaturation of fluid components (blood, lymph, and cerebrospinal fluid) with oxygen under pressure can enhance the delivery of oxygen and overcome the cerebral hypoperfusion that is creating the secondary injury. In 2009, we initiated an ongoing pilot study of HBOT in 6 U.S. servicemen with TBI/PTSD; the following case describes the history, treatment, and outcomes of one patient enrolled in the study.

History and Presentation

A 22-year-old male Army veteran served in Operation Iraqi Freedom between August 2006 and July 2007, with daily duties of route clearance as part of a Quick Reaction Force team. He had experienced approximately 40 IED blasts; daily headaches and seizures accompanied the last 2 or 3 exposures. He was medically evacuated in August 2007 and brought to Landstuhl Regional Medical Center, Germany, for further examination. On admission, he experienced 2 additional

seizures. There was no family history of epilepsy; CT of the brain was negative for bleeding, shift, and fracture; and EEG and MRI results were within normal limits. Evaluation revealed major depressive disorder, PTSD, pseudoseizure disorder, conversion disorder, and tinnitus. The final diagnosis was suspected mild TBI, and additional follow-up with neurology and behavioral health practitioners was recommended.

The patient's VA records documented 9 pseudoseizures within one month of returning to the United States. In September 2007, he experienced auditory hallucinations and headaches that started at the back center of his head and radiated to the right to left frontal lobes. One practitioner opined that the daily headaches were likely caused by prior analgesic misuse. The patient's records also indicated that he had memory problems, photophobia, phonophobia, osmophobia, and irritability. He did not receive a follow-up MRI, EEG, or CT.

The patient saw a psychiatrist, attended therapy sessions, and was prescribed various combinations of medications, including a period in which he received 7 drugs simultaneously. Medications included trazodone, venlafaxine, risperidone, quetiapine, sertraline, citalopram, eszopiclone, zolpidem, clonazepam, fluoxetine, amitriptyline, lorazepam, prazosin, propranolol, and promethazine.

In October 2007, he spent 12 days in a psychiatric hospital for extremely violent behavior after experiencing auditory hallucinations, homicidal ideation, and blackouts. He was diagnosed with PTSD, suicidal ideation, and dissociative disorder. In December 2007, he was institutionalized for 7 days after attempting suicide by ingesting 12 trazodone (5 mg) and 8 risperidone (1 mg). He was subsequently diagnosed with conversion disorder, convulsions, and alcohol abuse. In 2008, he experienced 2 to 5 pseudoseizures per week, headaches, anxiety, and upper body spasms. In February 2009, the patient was medically discharged with a 70%

disability rating. He began drinking heavily and joined a voluntary alcohol rehabilitation program.

When first seen at our facility in October 2009, the patient had PTSD; depression; posttraumatic nightmares 4 times per week; memory problems; high levels of frustration; painful, frequent headaches; and balance difficulties. His medications were venlafaxine, risperidone, mirtazapine, and topiramate. Neuropsychological evaluations included the Medical Symptom Validity Test, State-Trait Anxiety Inventory, Beck Depression Inventory–II, PTSD Checklist– Civilian Version, Neuropsychological Assessment Battery (NAB) Form 2 (attention, language, spatial, memory, and executive modules), and Personality Assessment Inventory. Initial testing with the NAB showed average or better range scores for all modules, whereas his other test scores indicated impaired psychological functioning.

Technetium-99m single-photon emission computed tomography (SPECT) brain scans (29.4 mCi) were obtained to document perfusion/metabolism brain abnormalities. The patient had abnormal SPECT brain scans at his initial evaluation (Figure 1A). The scans showed marked abnormalities in the frontal and parietal regions and in cerebellar areas, with greater abnormalities on the right side, in areas responsible for the visual-spatial abilities that allow individuals to navigate through both familiar and unfamiliar environments. Basal ganglia showed significantly decreased localization, and all areas of abnormal localization had peri-ischemic penumbra; the ventricles appeared slightly enlarged. Abnormal SPECT images correlated with the patient's decreased functional capacity measured in the psychiatric and physical evaluations.

Treatment

Treatment consisted of 40 sessions of hyperbaric oxygen exposure at 1.75 to 2 atmospheres absolute (ATA), delivered for 90-minutes, twice a day, 5 times per week, with 3 to 4 hours between exposures. Aggressive physical therapy, including vestibular stimulation for balance disorders and electrical stimulation and manual therapy for muscle and joint pain, was provided. No additional medications were prescribed.

Post-treatment Evaluation and Follow-up

Compared with baseline test results, neuropsychological evaluation at completion of treatment demonstrated significant improvements in depression, anxiety, and PTSD symptoms, including absence of nightmares and increased memory function (Tables 1 and 2). Significant improvements were also found in language function. Attention, spatial, and executive functioning were roughly equivalent to baseline.

Post-treatment SPECT brain scans revealed improvement in the cerebral cortex and cerebellar areas (Figure 1B). Areas of abnormality in the frontal and parietal regions were again greater on the right than the left. There was minimal decreased localization in the cerebellar area, again, with abnormalities greater on the right. Basal ganglia showed minimal abnormality with minimal-to-moderately decreased localization. All areas of abnormal localization continued to show peri-ischemic penumbra. The SPECT scans also suggested that although the ischemic penumbra was diminished, there were some areas of potentially recoverable brain tissue (PRBT), defined as viable but metabolically lethargic and electrically non-functional.

The patient reported feeling less depressed and more energetic, and had an improved appetite and fewer and less painful headaches. The patient's mother noted significant

improvements in mood, sleeping patterns, conversational skills, memory function, and level of alertness. Within 2 months of treatment completion, he enrolled in a local college; by the end of the semester, he had earned a 3.6 G.P.A. He had also stopped taking any prescription medications.

The patient's post-treatment scores relative to pre-treatment scores were significantly better for measures of depression, PTSD, anxiety, attention, language and memory. At the 10month follow-up, he scored significantly better relative to post-treatment scores for measures of depression, PTSD, anxiety, and spatial function (Tables 1 and 2). His 10-month NAB Language module score was equivalent to baseline and post-treatment scores, and while the decrease in the NAB Memory module score was not significantly different versus the post-treatment score, it was significantly better than at baseline.

Discussion

IED-induced blast injuries sustained by soldiers include contusion, edema, hemorrhage, diffuse axonal damage, and damage to neurons and glia.^{21,22} Interestingly, Swedish researchers demonstrated that exposure to machine gun and anti-tank fire caused damage equivalent to that associated with decompression illness in SCUBA divers,²³ which may help explain the increased incidences of suicide among blast-exposed veterans and patients suffering from decompression illness.

Successful treatment of TBI is complicated by compromised cognitive abilities; if a patient can neither focus on physical or mental tasks during therapy nor retain information or remember to take prescribed medications, progress toward wellness can be extremely challenging. Traditional treatment approaches to TBI address each symptom separately: various

medications are used to treat sleep disorders, depression, emotional issues, and pain; psychotherapy is used to address emotional problems; and physical therapy is applied to recover motor skills. Patients must follow complicated usually ineffective regimens—as well as endure associated adverse effects—and can become increasingly frustrated.

The pathophysiology of TBI-induced brain injury involves the volume of the infarct (umbra) in the region of brain injury and a variable volume of peri-infarcted tissue of diminished blood flow (ischemic penumbra) where a differential sensitivity of brain tissue function exists based on oxygen availability.^{9-11,16,24} In hypoxia, the critical oxygen tension ($P_C O_2$) is the partial pressure of oxygen (PO_2) at which oxygen consumption (VO_2) is below the normoxic control. In penumbral areas where the blood flow is below 10-15 mL/100 g brain tissue, neurons and possibly glial cells enter an idling state.^{13,24} "Idling neurons" (IN) in the ischemic penumbra are viable but show decreased metabolism and no electrical activity.¹³ IN are difficult to detect by standard neurological techniques because they behave as if they are non-viable, yet they represent PRBT, or areas that can be reactivated by increased oxygen availability.¹³ Comparison of pre- and post-HBOT SPECT scans provide tangible evidence of PRBT and can be used to follow the course of therapy and help identify end points of therapy.^{13,17-19,25} The patient's SPECT scans were consistent with the presence of PRBT, its diminution with HBOT, and its positive correlation with psychological, cognitive and physical improvements after therapy. The post-treatment scans also showed residual PRBT and thus the potential for further recovery if treatment were continued.

Unlike symptom-focused treatment strategies for TBI, which may not address the underlying pathological processes of cerebral neuronal and glial injury, HBOT offers myriad physiological, cellular, and biochemical effects and targets the source of the impairment by

facilitating the reactivation and repair of neurons and glia through improved oxygenation and blood flow in the brain.^{13,14,18,19}

Conclusions

In this patient, HBOT was successful in alleviating TBI/PTSD symptoms by repairing brain damage sustained from blast injury without any adverse effects. SPECT brain imaging documented brain abnormalities prior to HBOT and objectively confirmed the response to HBOT and physical therapy. HBOT may benefit TBI/PTSD patients by reducing or eliminating the confusion and side effects associated with complex pharmacologic regimens. A larger clinical study sponsored by the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury and the Army Research and Materiel Command started enrolling patients in January 2011 (NCT01306968). The trial will examine the effects of 40 HBOT sessions in approximately 300 U.S. servicemen who experienced a TBI with persistent symptoms (>4 months) during deployment.

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Figure Legends

Figure 1. Three-dimensional composite of anterior, posterior, and lateral views of SPECT brain scans. **(A)** Baseline scans showing a markedly abnormal patchy-type pattern of localization in both cerebral hemispheres, with the greatest abnormality in the frontal and parietal regions bilaterally and with greater abnormality on the right than on the left. There was also a pattern of decreased localization in both cerebellar areas, again greater on the right than on the left. **(B)** Post-treatment scans showing a minimally abnormal patchy-type pattern of localization in both cerebral hemispheres involving the frontal and parietal areas and with greater abnormality on the right than the left. There was also some minimally decreased localization in both cerebellar areas, again greater on the right the post-treatment scans, the post-treatment scans show significant improvement in both cerebral hemispheres and cerebellar areas, with minimal abnormality noted, though still greater on the right than on the left.

Tables

Table 1. Psychological evaluation raw scores at baseline (T1), post-treatment (T2), and 10-week

follow-up (T3)

Total

				Change					
	T1	T2	T3	T1 to T2	T2 to T3	T1 to T3			
Beck Depression Inventory- II (BDI-II) Score ^a	31	14	4	-17	-10	-27			
Post-Traumatic Stress Disorder Checklist–Civilian Version (PCL-C) Score ^b	68	40	30	-28	-10	-38			
State-Trait Anxiety Inventory (STAI)-State Score ^c	50	40	34	-10	-6	-16			
STAI-Trait Score ^c	65	48	45	-17	-3	-20			
Neuropsychological Assessment Battery Form 2 ^d									
Attention	101	107	108	+6	+1	+7			
Language	135	145	137	+10	-8	+2			
Memory	96	116	108	+20	-8	+12			
Spatial	112	105	118	-7	+13	+6			
Executive	113	110	114	-3	+4	+1			

^a Scoring ranges from 0 to 63; scores above 30 indicate severe depression.

115 122

^b Scoring ranges from 17 to 85; scores above 30 indicate PTSD, changes of 10 or more are considered significant.

123

+7

+1

+8

^c Scoring ranges from 20 to 80; the higher the score, the greater the anxiety level.

^d Scoring ranges include: 69 and below, extremely low; 70 to 79, borderline; 80 to 89, below average; 90 to 109, average; 110 to 119, high average; 120 to 129, superior; and 130 and above, very superior.

Table 2. Personality Assessment Inventory (PAI) scale T-scores^a at baseline (T1), post-treatment (T2), and 10-week follow-up (T3)

				Change		
Scale	T1	T2	T3	T1 to T2	T2 to T3	T1 to T3
Somatic complaints	82	78	69	-4	-9	-13
Anxiety	87	72	64	-15	-8	-23
Anxiety-related disorders	87	78	65	-9	-13	-22
Depression	82	54	55	-28	+1	-27
Mania	74	89	68	+15	-21	-6
Paranoia	69	62	53	-7	-9	-16
Schizophrenia	77	63	54	-14	-9	-23
Borderline features	90	82	67	-8	-15	-23
Antisocial features	67	79	63	+12	-16	-4
Alcohol problems	61	72	57	+11	-15	-4
Drug problems	62	50	50	-12	0	-12
Aggression	76	75	66	-1	-9	-10
Suicidal ideation	64	60	54	-4	-6	-10
Stress	68	73	53	+5	-20	-15

^a Raw scores are transformed into T-scores, which have a mean of 50 and a standard deviation of 10 compared with a standardization sample; decrease in score indicates improvement.

Figures

Figure 1

