



EEG-based brain biomarker supports hyperbaric oxygen therapy for acute concussions

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ABSTRACT

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Acute concussion is a significant health issue among youth athletes, affecting their quality of life and performance. However, the standard of care, rest, has been questioned, while treatments are lacking. This pilot case series used an FDA-cleared electroencephalogram-based brain biomarker (EEGBB) to demonstrate hyperbaric oxygen therapy (HBO₂) improvement for treating concussion. From December 31, 2021, through May 27, 2022, school-aged patients presenting at two HBO₂ clinics within ten days of injury with an acute concussion confirmed by an initial EEGBB assessment were evaluated. The EEGBB diagnoses concussions using artificial intelligence to yield a score between 0-100, with scores ≤70 considered concussed. HBO₂ using 1.5-2.0 ATA, progressing stepwise per patient tolerance, was administered in ≥4-hour intervals until sustained symptom-free. EEGBB assessment was performed before and after each treatment. Eleven patients [mean age: 16±2.2; six male (55%)] participated. Patients presented one to nine days (median: three) after injury. Their median baseline EEGBB score was 18 (range: 1 to 35). The median first and last post-treatment scores available were 84 (range: 32-90) and 85 (range: 75-89), respectively. The median number of HBO₂ treatments was three (range: 2-8) administered over a median of two days (range: two to five). All patients except one (due to a technical error) received a post-treatment follow-up score 2-22 days after treatment completion. The median final score was 85 (range: 64-90). There were no adverse events. Preliminary data demonstrate that the EEGBB objectively supports the use of HBO₂ to treat acute concussions. Further research should confirm the appropriate HBO₂ regimen to treat concussions.

Keywords: Hyperbaric oxygen therapy; mild traumatic brain injury; student-athletes

INTRODUCTION

Concussions, or mild traumatic brain injuries (TBIs), result in 2.8 million annual emergency department visits, hospitalizations, or deaths and an additional 845,000 outpatient pediatric cases in the United States (US) [1-3]. The US Centers for Disease Control and Prevention (CDC) defines a concussion as a bump, blow, or jolt to the head, or a hit to the body that causes the head and brain to move rapidly back and forth [4]. Concussions are functional brain injuries that undergo an “energy crisis” [5]. Oxygen-de-

pendent metabolism of glucose fuels brain energy. When a patient is concussed, the brain cells need greater than normal blood flow to correct the energy crisis, but this blood flow is decreased for seven to ten days after injury [5]. Presently, there is no treatment available to resolve concussions among youth. Concussions are managed mainly with one to two days of acute rest with subsequent gradual and progressive return to activity, a standard of care supported by very limited evidence [5,6].

Literature, including the 2022 Consensus Statement on Concussion in Sport, has increasingly questioned the adequacy of acute rest as the standard of care for concussion [6-17]. The authors of the 2022 Consensus statement acknowledge that cervicogenic symptoms such as migraines, cognitive impairment, and balance and motor disorders require management, and when symptoms persist beyond four weeks in pediatric patients, collaborative care with rehabilitation may be necessary [6]. Multiple studies have demonstrated that participating in physical activity within a few days of injury was associated with a shorter recovery and reduced risk of post concussive syndrome (PCS; defined as having more than three concussive symptoms, such as feeling slowed down, headache, noise sensitivity, and fatigue, 28 days after injury) than conventional management [11-14,18]. However, one should interpret the findings that advocate for an early return to school with caution, as the unit used to define early return is the number of missed school days and not the number of days students rested. For example, in a recent, large comparative study of pediatric patients with acute concussion who returned to school after missing only two school days ($n = 875$) or returned after missing at least three school days ($n = 546$), the early return group reported accelerated recovery [19]. Since weekend days were not counted as missed “school days,” most of the early return group ($n = 546$, 62.4%) had a concussion occurring on Wednesday through Saturday, which implies that they could have missed only two days of school but rested for four days over the weekend [19].

Mounting evidence supports that there are long-term effects of concussion, especially in teenagers, who demonstrate altered cerebral function and motor control [20]. One out of five adolescents (aged 12 to 15 years) have subsequent concussions within two years of their first concussion and are therefore at risk for long-term health and developmental consequences [21]. Among 230 children (mean age: 14.8 years) presenting with an acute concussion within ten days of injury, 133 (58%) experienced PCS [22]. Furthermore, the CDC reported that 14% of pediatric patients with a mild TBI struggled with academic performance one year after injury [4].

The US Food and Drug Administration (FDA) approves hyperbaric oxygen therapy (HBO₂) as a safe and effective treatment of acute arterial ischemia, thermal injuries, acute retinal artery occlusion, crush injury, compartment syndrome, and for the healing of refractory wounds [23]. During the early period following injury, HBO₂ supplies oxygen to hypoxic tissues lacking adequate perfusion. HBO₂ could provide the energy the brain tissue needs to resolve its energy crisis and repair the damage [23,24]. HBO₂ also decreases edema and resolves inflammation.

Over the past three decades, the reluctance of the medical community to apply HBO₂ to TBIs (mostly with PCS) stems from controversial evidence that was generated from poorly designed clinical trials with mischaracterized shams, variable dosing effects, small sample sizes, and design bias leading to misunderstandings over the beneficial therapeutic effect of HBO₂ on TBI with PCS [1]. Much of the confusion in historic HBO₂ trials concerns the traditional definition of HBO₂, which uses an arbitrary threshold, with the patient breathing 100% oxygen at 1.4 atmospheres absolute (ATA) [1,23,25,26]. By that definition alone, any pressure lower than 1.4 ATA is not considered HBO₂, when lower doses still have a beneficial effect. An updated scientific definition focuses on HBO₂ as a combination gene therapy that utilizes increased total atmospheric pressure and increased partial pressure of oxygen to express or suppress up to 8,101 genes [1,27-29]. Reviews and systematic reviews consistently demonstrate that in all studies evaluating HBO₂ on TBI and PCS, 1.5 ATA resulted in significant symptomatic and/or cognitive improvements in patients with TBI [1,25,26]. In China, HBO₂ has emerged as the recommended treatment for craniocerebral injury, and two recent comparative trials demonstrate that HBO₂ accelerates cognitive recovery in adult patients [30,31].

To further clarify the therapeutic effect of HBO₂ on concussions, an objective method to assess HBO₂ is needed. In September 2019, the FDA cleared an electroencephalogram-based brain biomarker (EEGGB) for adjunctive use in closed head injury that objectively diagnoses concussions at the point of care. The device uses artificial intelligence based on a genetic algorithm methodology that incorporates

linear and nonlinear features of the EEG with clinical symptoms and neurocognitive, vestibular, and balance measures, and a discriminate reaction time to yield a score of 0-100 to assess brain function, with scores of 70 or lower diagnostic of a concussion [32-38]. Multiple studies have evaluated and validated the use of the EEGBB in youth and student athletes [32-38]. In a large validation study of 580 young athletes (aged 13 to 25 years), 207 (35.7%) of whom had concussion, the diagnostic score had a sensitivity of 86.0% [95% Confidence Interval (CI): 80.5%-90.4%], specificity of 70.8% (95% CI: 86.1%-93.3%), and a negative predictive value of 90.1% (95% CI: 86.1%-93.3%), and a positive predictive value of 62.0% (95% CI: 56.1%-67.7%) [38].

This pilot case series used the EEGBB to objectively demonstrate that acute concussions in youths were resolved following HBO₂ treatment. The study hypothesis is that HBO₂ improves symptoms and resolves acute concussions in youths.

MATERIALS/SUBJECTS AND METHODS

This retrospective case series took place at two HBO₂ clinics in Northbrook, IL, and Fargo, ND, where patients with acute concussions have been treated with HBO₂ since 2016 and 2018, respectively. Due to the exploratory nature of this pilot study, there was no predetermined sample size. Preliminary outcomes data from this study will be used to design a stronger, larger trial in the future. The primary endpoint was symptom improvement following HBO₂, as determined by the number of patients sustained symptom-free following HBO₂, with EEGBB scores in the non-concussed range (>70). Secondary endpoints included the number of HBO₂ treatments needed, the duration of treatment (number of days), and the time to heal from the onset of injury (defined as the number of days after the injury when HBO₂ was completed and the patient was sustained symptom-free), and the safety of HBO₂, based on the incidence of adverse events. Sustained symptom-free was defined as when patients could return to school, return to participate in sports fully, and have unlimited screen time without experiencing any symptoms related to concussion, such as headache, brain fog, confusion, and fatigue. The study

protocol (No. 20223720) adhered to the ethical standards of the WCG IRB (Puyallup, Washington), which retrospectively approved a request for a waiver of authorization for use and disclosure of protected health information on July 15, 2022.

School-aged patients, including college/university students, who presented at the study clinics with a symptomatic, acute concussion were considered eligible for enrollment, provided that they or their parents provided their written informed consent to undergo HBO₂ and their oral consent to have their EEGBB data used for research purposes in a manuscript. Study exclusion criteria included having a concussion that occurred more than ten days prior to the first visit or having an acute-on-chronic concussion (if a patient was newly concussed but still had not resolved symptoms of a previous concussion). Screening and patient enrollment began on December 31, 2021, and the study concluded with the final follow-up visit on May 27, 2022.

Upon informed consent, patients were enrolled in the study and underwent their first EEGBB assessment. Immediately prior to the EEGBB assessment, the provider assessed the patient using the Glasgow Coma Scale (GCS) score and inputted their GCS score into the EEGBB system. The EEGBB (Brainscope®, Brainscope Company, Bethesda, MD) involves wearing a single-use, disposable, noninvasive headset that a patient has on for approximately ten minutes while lying supine to collect EEG brainwaves. The patient then performs a discriminate reaction time test on the handheld device while wearing the headset. Figure 1A-1E depicts a patient using the EEGBB before and after a HBO₂ session, with the device screenshots provided. The machine analyzes the brainwaves with other factors using artificial intelligence to generate a score between 0 and 100. A score of 70 or lower indicates that the patient has a concussion, and a score of 25 or lower indicates a severe concussion [39]. The first pretreatment EEGBB assessment score confirmed the concussion diagnosis. Baseline data were collected from the initial EEGBB assessment via a device-generated, digital summary report containing the initial score, patient demographic information and history of prior concussion, clinical signs and symptoms, the GCS score;

whether or not the patient loss consciousness at the time of injury; whether or not the patient had a headache, dizziness, or balance issues at the time of assessment, and whether or not the patient had been disoriented, had retrograde amnesia, or had altered mental state after the injury occurred. Patients then proceeded with HBO₂.

The supervising hyperbaric physician administered HBO₂ in a monoplace chamber using 1.5-2.0 ATA, progressing stepwise per the patient's tolerance, for 70 minutes. Treatments were ideally administered twice daily (with at least a four-hour interval) until symptom-free, based on the clinics' experience and the implementation of twice-daily treatment sessions for other HBO₂ indications, such as compartment syndrome [40]. Intervals between treatments could have varied due to the long distances possibly traveled or the schedules of the patients' families. Before and after each treatment session, the patient underwent an EEGBB assessment and reported the presence/absence of concussive symptoms and if any adverse events or reactions, such as barotrauma, occurred. HBO₂ was administered until the patient was sustained symptom-free. Ideally, each patient should have had at least one pretreatment and post-treatment EEGBB score greater than 70. From previous experience, patients notably feel improvements post-treatment, until their concussion is resolved. In this case series, patients received treatment until they no longer reported feeling any improvement post-treatment. Some patients requested additional treatment for various reasons,

mainly because they traveled far from home and did not want to have to return again to the clinic. A follow-up EEGBB was performed at least two days after completing their last HBO₂ treatment session to confirm that the EEGBB correlated with the patient's sustained symptom-free status.

The principal investigator collected all the study data from patients' medical records and imputed them into an Excel spreadsheet for analysis. Continuous variables were presented as means, ranges, and standard deviations (SDs); nonnormal data were summarized using medians. Categorical variables were summarized as counts and proportions or percentages. Missing follow-up data were addressed with the last observation carried forward principle. All study data are published in this article.

RESULTS

Eleven patients (six male, 55%) presented to the study clinics (eight in Fargo, ND, and three in Northbrook, IL) with an acute concussion caused by sports injury; all were eligible and enrolled in the study. Table 1 summarizes the patients' baseline characteristics. Their mean age was 16±2.2 years; range 14-21 years. Their first visit occurred one to nine days after injury (median: three days). All patients had a GCS score of 15 confirmatory for concussion. Five patients (45%) had a prior concussion. Their median baseline EEGBB score was 18 (range: 1-35). Only two patients presented with an EEGBB score greater than 25; therefore, nine met the "severe concussion" criteria determined by the EEGBB. In Table 1, the pres-



Figure 1A-1E. A patient with acute concussion takes an initial electroencephalogram-based brain biomarker (EEGBB) assessment (Figure 1A), which confirms on the mobile handheld device (screenshot provided in Figure 1B) that the patient has a concussion with a score of 24. The patient next undergoes treatment in a hyperbaric oxygen chamber using 1.5-2.0 ATA, progressing stepwise per patient's tolerance, for 70 minutes (Figure 1C). He then undergoes a posttreatment EEGBB assessment (Figure 1D), obtaining a nonconcussed score of 89 (device screenshot provided in Figure 1E). After ≥4 hours, the patient will repeat treatment and EEGBB assessment until he is sustained symptom free (not shown). The patient provided their written informed consent that their photographs may be used in this publication.

ence of symptoms did not necessarily correspond to the severity of the EEGBB score. For example, Patient 2 only reported having a headache as a symptom of concussion, but her baseline EEGBB score was a very low 20, indicative of a severe concussion.

All patients underwent HBO₂. Table 2 summarizes the available EEGBB scores before and after each HBO₂ session throughout the study for each patient. Some EEGBB scores were unavailable due to technical issues (when the device was inadvertently left uncharged) or due to supply issues, when the individual headsets underwent shipping delays and did not arrive on time for the patient's visit. The median number of HBO₂ treatments given was three (range: 2-8), and the treatment period lasted a median of two days (range: two to five). All patients' median first posttreatment EEGBB score was 84 (32-90). The first post-treatment score of six patients (54.5%) was greater than 70 and, therefore, in the non-concussed range. Among these six patients, five remained symptom-free by their second treatment, but Patient 1 (Figure 2) returned for her second treatment three days later with a pretreatment concussed score of 39.

Interestingly, she went to school after her second treatment and returned later that day with a score of 13, lower than the 39 she presented earlier. After her third treatment, she presented the next day; only four days after her injury, she presented symptom-free. Patient 2 (Figure 3) had a severe concussion, with a baseline EEGBB score of 20, which resolved after only one treatment and remained symptom-free after 15 days. Patient 7 (Figure 4) had pretreatment scores in the concussed range until she came for her sixth treatment on Day four, and Patient 8 needed seven treatments before he had a pretreatment non-concussed score of 88 on Day 5, after which he was sustained symptom-free (Table 2). All patients' median last post-treatment score was 85 (range: 75- 89). All patients were symptom-free upon completion of HBO₂; treatment ended two to ten days (mean: 5.2±2.3) after injury. No adverse events or reactions were reported during this study.

All 11 patients returned for a follow-up EEGBB evaluation a median of 14 days after injury (range: 10-26) and eight days after completing HBO₂ (range: 2-22). Ten patients obtained a follow-up EEGBB score; no score was obtained for Patient 8 because

variable	patient 1	patient 2	patient 3	patient 4	patient 5	patient 6	patient 7	patient 8	patient 9	patient 10	patient 11
sex	f	f	m	m	m	f	f	m	m	f	m
age, years	15	19	21	16	14	14	16	16	15	18	17
PID of first visit	1	9	3	3	6	3	2	1	1	7	1
prior concussion	no	no	yes	yes	yes	no	yes	yes	no	no	no
loss of consciousness	no	no	no	no	yes	no	no	no	no	no	no
at time of baseline EEGBB assessment											
headache	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes
dizziness	yes	no	no	yes	no	yes	yes	no	yes	yes	no
balance issues	no	no	no	no	no	yes	no	no	no	no	no
since injury, has been											
disoriented	yes	no	no	no	yes	no	no	no	yes	yes	yes
retrograde amnesia	yes	no	no	yes	yes	no	yes	no	yes	no	no
altered mental status	no	no	no	no	no	no	no	yes	yes	yes	yes
GCS score	15	15	15	15	15	15	15	15	15	15	15
baseline EEGBB score	2	20	35	18	28	1	10	25	3	24	4
Electroencephalogram-based brain biomarker (EEGBB); GCS = Glasgow Coma Scale; PID = postinjury day											

Table 1. Patient baseline characteristics. All presented with acute concussion.

	patient 1	patient 2	patient 3	patient 4	patient 5	patient 6	patient 7	patient 8	patient 9	patient 10	patient 11
1st HBO₂ treatment											
PID	1	9	3	3	6	3	2	1	2	7	1
pre-HBO ₂ score	2	20	35	18	28	1	10	25	3	24	4
post-HBO ₂ score	84	86	84	90	88	N/A	66	38	32	47	75
2nd HBO₂ treatment											
PID	4	10	4	3	6	3	2	1	2	7	1
pre-HBO ₂ score	39	83	78	87	88	59	4	16	75	47	81
post-HBO ₂ score	83	80*	84	92	80	85	90	44	78*	83	72
3rd HBO₂ treatment											
PID	4		4	4	7	5	3	2		8	2
pre-HBO ₂ score	13		79	78	55	79	37	11		87	45
post-HBO ₂ score	89		85*	86*	87*	87	84	40		82*	78
4th HBO₂ treatment											
PID	5					5	3	2			3
pre-HBO ₂ score	92					87	54	14			75
post-HBO ₂ score	88*					N/A*	86	58			N/A*
5th HBO₂ treatment											
PID							4	3			
pre-HBO ₂ score							35	N/A			
post-HBO ₂ score							85	88			
6th HBO₂ treatment											
PID							4	3			
pre-HBO ₂ score							72	N/A			
post-HBO ₂ score							79*	84			
8th HBO₂ treatment^a											
PID								5			
pre-HBO ₂ score								89			
post-HBO ₂ score								N/A*			
follow-up											
PID	13	15	13	10	14	20	26	24	12	10	14
follow-up score	89	85	90	88	90	79	73	N/A	70	64	84

^aPatient 8 was the only patient who required >6 HBO₂ treatments, but data were missing for his seventh treatment 4 days after injury occurred, due to a technical error.

N/A = EEGBB score data not available due to a technical error; PID = post-injury day

Table 2. Electroencephalogram-based brain biomarker (EEGBB) scores before and after each hyperbaric oxygen therapy (HBO₂), per patient. Asterisks indicate when patient was determined to be sustained-symptom free and would no longer need HBO₂ treatment.

the EEGBB was not charged at the follow-up visit. The median final score was 85 (range: 64-90), with all patients still sustained symptom-free. Patient 10 had a concussed follow-up score of 64, but she was symptom-free and returned to play the next day without complications or complaints.

DISCUSSION

Nearly half of the current study population had a previous history of concussion. Among 177 brains with chronic traumatic encephalopathy (caused by repeated head trauma) donated for scientific research, nearly 30% (n = 51) were from deceased student athletes [41]. The long-term consequences

of TBI in youth sports are real. It is time to move beyond inadequate management of concussions and acknowledge that rest alone is not sufficient to resolve head trauma. Preliminary data from this pilot case series demonstrate that the EEGBB assessment supports the hypothesis that HBO₂ resolves acute concussions when applied to a student population within ten days of injury. A recent case series evaluating the use of HBO₂ in 17 adults with mild and moderate TBI reported that 40 treatments administered five times weekly resulted in significant symptom improvement ($p < .05$) [42]. In the current study, only a median of three treatments were needed over two days to confirm that pediatric patients were symptom-free. HBO₂ was a quick, efficient, and beneficial treatment for all patients with TBI, including those with severe concussions. HBO₂ was also a safe treatment in this student population, with no adverse

events or reactions reported. All patients completed the study symptom-free. The EEGBB objectively demonstrated that clinical symptoms, which are self-reported and subjective, [38] do not correspond to the severity of concussion (as shown in Table 1). While most patients appeared better after just one HBO₂ session, for the majority ($n = 6$, 54.5%), feeling better and/or being symptom-free after just one treatment was an intermittent health state. These patients returned for their next visit with symptomatic concussion. Therefore, it is essential to continue treating patients with additional HBO₂ sessions until they report being sustained symptom-free.

This study was limited by its noncomparative, uncontrolled design and small sample size. However, most of the patients presented for HBO₂ within three days of injury ($n = 8$, 72.7%) and had severe concussion ($n = 9$, 81.8%). Further study of a large

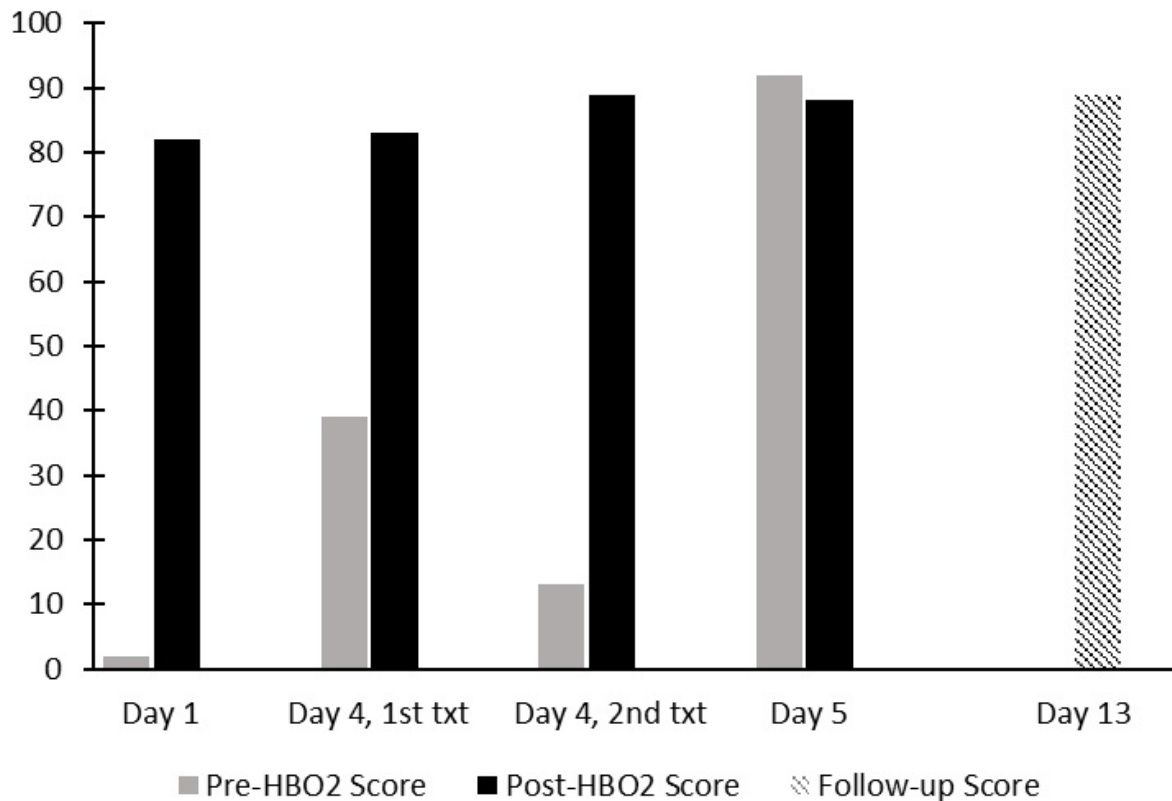


Figure 2. Summary of electroencephalogram-based brain biomarker (EEGBB) scores before and after hyperbaric oxygen therapy (HBO₂) for Patient 1, a 15-year-old female student who underwent four treatments (txts). She first presented one day after injury with a baseline EEGBB score of 2, indicating severe concussion. She underwent one treatment that day, after which her EEGBB score increased to 84. She returned three days later with a low, concussed score of 39 and underwent two treatments, finishing with a score of 89. She had one final treatment five days after injury, and her final post-treatment score was 88. She returned for a follow-up evaluation 13 days after injury (eight days post-treatment), and her EEGBB score was 89.

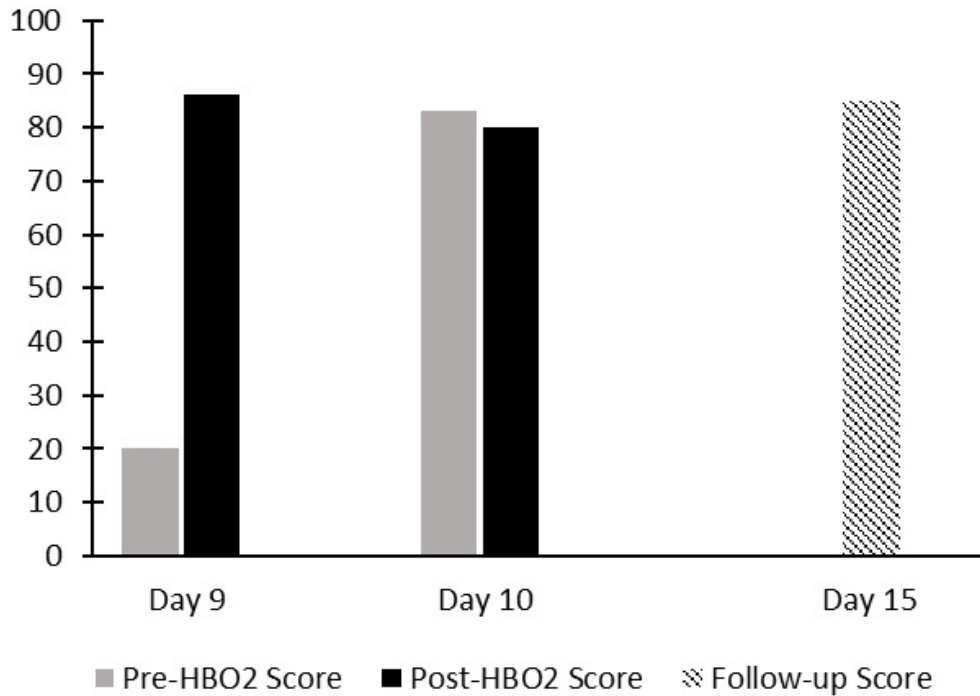


Figure 3. Summary of electroencephalogram-based brain biomarker (EEGBB) scores before and after hyperbaric oxygen therapy (HBO₂) for Patient 2, a 19-year-old female student who underwent two treatments (txts). She first presented nine days after injury with a baseline EEGBB score of 20, indicating severe concussion. She underwent one treatment that day, after which her EEGBB score increased to 86. She returned one day later for a second treatment, finishing with a score of 80. She had a follow-up evaluation 15 days after injury (five days post-treatment), and her EEGBB score was 85.

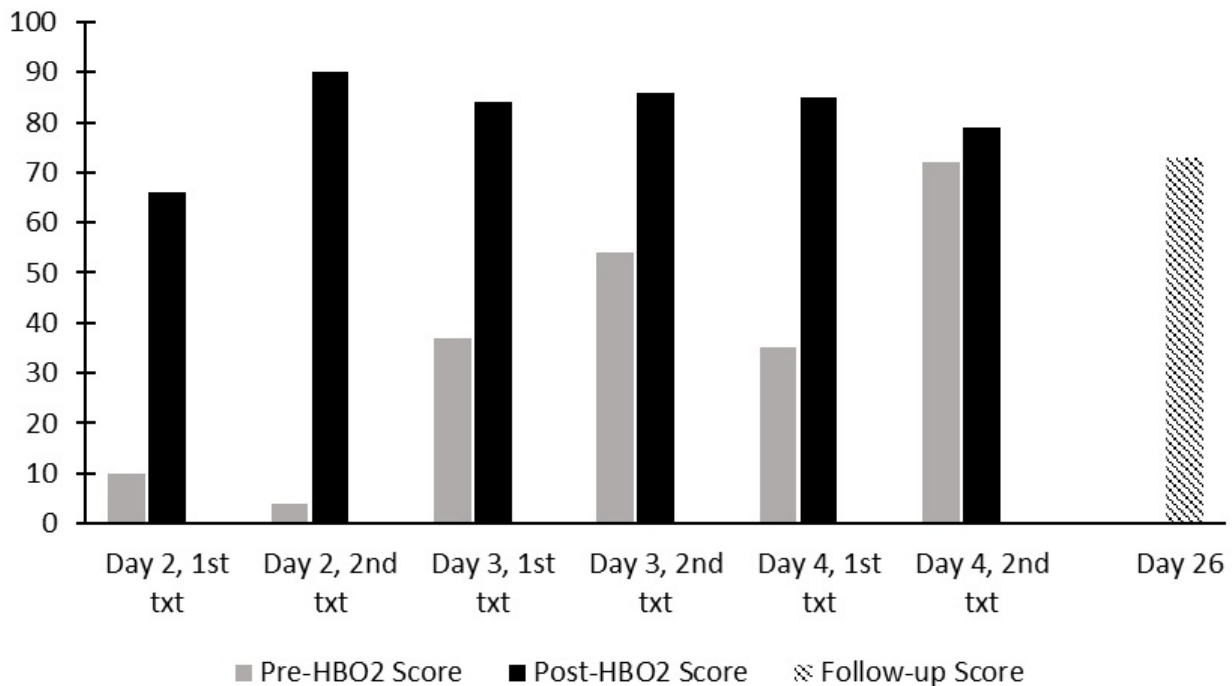


Figure 4. Summary of electroencephalogram-based brain biomarker (EEGBB) scores before and after hyperbaric oxygen therapy (HBO₂) for Patient 7, a 16-year-old female student who underwent six treatments (txts). She first presented two days after injury with a baseline EEGBB score of 10, indicating severe concussion. She underwent two treatments that day, after which her EEGBB score increased to 90. She returned one day later for two treatments, after which her score was 86. She returned four days after injury for two more treatments, finishing with a score of 79. She had a follow-up evaluation 26 days after injury (22 days post-treatment), and her EEGBB score was 73.

sample in a more controlled environment is warranted to analyze whether earlier treatment with HBO₂ mitigates the overall severity of concussion (as measured by the EEGBB), compared to patients treated with only standard concussion management, and whether more treatments are needed for more severe concussions. The HBO₂ dosing regimen (1.5-2.0 ATA) used in this pilot study is consistent with the updated scientific definition of HBO₂ and reviews of HBO₂ dosing evidence for TBI [1,25,26], but further study is also needed to confirm the HBO₂ protocols to treat TBI in student athletes.

Although the EEGBB is the only FDA-cleared device that can objectively diagnose and assess concussion, its predictive limitations in giving false negatives and false positives are reported in some patients [25]. In the current study, Patient 10 had a low follow-up EEGBB score of 64, likely a device technical error, as she was symptom-free. Some EEGBB scores were not provided or were missing (Table 2) due to technical and supply errors, so a clinical evaluation should still be performed to confirm that the patient is symptom-free.

This HBO₂ study supports the idea that supplying oxygen under increased atmospheric pressure solves the “energy crisis” of a concussion [4,23,24]. After TBI occurs, microglia are activated, inflammatory cytokine production is increased [43], and vasculature is altered with decreased complexity observed [44]. Resultant gray and white matter wounds progress and cause loss of downstream synapses, neurons, and tissue with impaired function [25,26,44-54]. In PCS, chronic brain wounding is documented [1,55-57]. Not a single TBI treatment targets the biological wound repair of the brain other than HBO₂ [25,26]. Given its safe and effective application to chronic wounds and acute injuries, HBO₂

may be the first treatment that repairs and restores the compromised tissue of the acute TBI-injured brain [1,25,26,58].

The mechanisms by which HBO₂ restores healthy brain tissue have been under investigation. When HBO₂ is administered to an acute concussion, it appears to have a neuroprotective, anti-inflammatory effect by weakening microgliosis and cytokine expression [26]. HBO₂ also appears to increase blood flow to the brain [59]. Further study is warranted to elucidate the mechanism of action and application of HBO₂ to treat acute concussions.

Preliminary data from this small pilot case series demonstrated that HBO₂ safely and efficiently resolves acute concussions in student athletes, who quickly became sustained symptom-free. All patients resumed their full school and sports schedule, most within a few days of starting HBO₂, and have remained asymptomatic at the time of this writing. The EEGBB is an objective tool to diagnose concussion and to measure the impact of each HBO₂ treatment, as well as the durable repair HBO₂ provides for the acute concussion. Using the EEGBB with HBO₂ warrants further study to support a new paradigm to treat concussions. A larger, more controlled comparative study will confirm the appropriate HBO₂ regimen and treatment protocol.

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