

## HYPERBARIC OXYGEN THERPAY FOR CHRONIC COGNITIVE IMPAIRMENTS DUE TO TRAUMATIC BRAIN INJURY- RANDOMIZED PROSPECTIVE TRIAL

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**Introduction:** A common sequelae of mild traumatic brain injury(mTBI) is the so called postconcussion syndrome(PCS), a complex of symptoms that includes neuropsychiatric symptoms, and cognitive impairment. Even though the majority of patients will recover, 9-25% will have persistent symptoms<sup>1-4</sup>. In these patients hypoxia in the damage brain tissue plays a major role in the impaired regeneration/healing processes<sup>5</sup>. Recently, we reported that hyperbaric oxygen therapy(HBOT) can induced neuroplasticity in the chronic phase of post stroke patients<sup>6</sup> and the aim of this study was to evaluate the effect of HBOT on cognitive impairments and brain metabolism in chronic mTBI patients in a prospective, controlled, randomized, cross-over study.

**Methods:** The study included 90 patients who suffered from mTBI, 1-6 years prior to inclusion, and had complaints regarding their cognitive function. Patients were randomized into two groups: a treated group and a cross group. The patients in the treated group were evaluated twice: baseline and after HBOT. Patients in the cross group were evaluated three times: baseline, after control period of no treatment, and after HBOT. The HBOT protocol was: 40 sessions, 5 days/week, 90 minutes, 100% oxygen at 1.5ATA. The primary end points included neuropsychological function(Mindstreams testing battery), and brain metabolism, evaluated by SPECT. Secondary end point included quality of life evaluation. Evaluations were made by medical and neuropsychological blinded to patients' group.

**Results:** Following HBOT a significant improvement in all cognitive measures (memory, executive function, attention and information processing speed) as well as quality of life was observed in both groups after HBOT( $p < 0.005$  for all). No improvement was noticed in the crossed group during the control period.

Concomitantly, a significant improvement in brain metabolism was also demonstrated in the brain SPECT evaluation.

**Conclusion:** HBOT may induce significant neuroplasticity and improve cognitive function in patients with mTBI even years after the acute injury.

**Key words:** Hyperbaric oxygen, Traumatic brain injury, Prospective randomized control trial.

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## **Hyperbaric Oxygen Therapy for Chronic Cognitive Impairments due to Traumatic Brain Injury- Randomized Prospective Trial**

### **INTRODUCTION**

Approximately 1.74 million people sustain a traumatic brain injury (TBI) in the United States every year [1]. Most, 70–90%, are mild[2]. A common sequelae of mTBI, 30-80 percent, is the so called postconcussion syndrome (PCS), a complex of symptoms that includes headache, dizziness, neuropsychiatric symptoms, and cognitive impairment [3,4]. Even though the majority of patients will largely recover by three months, 9-25 percent will have persistent symptoms for more than 1 year [5,6,7,8,9,10]. Such individuals are at high risk for emotional and cognitive dysfunction, culminating in inability to carry out ordinary daily activities, work responsibilities and standard social relationships [7,8,9,10]. Unfortunately, currently, there is no effective treatment/metabolic intervention being used in the daily clinical practice for post mTBI patient's suffering from chronic neuro-cognitive dysfunction.

The primary mechanism of mild TBI injury involves diffused shearing of axonal pathways and small blood vessels, due to forces of acceleration-deceleration at the time of injury, also known as Traumatic Axonal Injury [11]. Other primary

mechanism, usually caused by a direct hit to the skull, include brain contusions, commonly involve the frontal and anterior temporal lobes [10]. Secondary mechanisms of mTBI includes ischemia, mild edema, and other bio-chemical and inflammatory processes culminating in impaired regenerative/healing processes due to worsening of tissue hypoxia[12]. Due to the diffused nature of injury, cognitive impairments is usually the predominant symptoms, involving deficiencies in several cognitive functions: primarily memory, attention, information processing speed, and executive function, all localized in multiple brain area, and, according their potent function relays on potent network structure and connectivity between different brain areas [10,13,14].

Hyperbaric Oxygen treatment (HBOT) is the inhalation of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA) in order to enhance the amount of oxygen dissolved in the blood and body fluids [15,16,17]. Since 1cm<sup>3</sup> of normal brain tissue contains about 1km of blood vessels, high oxygen supply is essential for repair of any damaged regions brain region. Indeed, as has been demonstrated by previous studies, an increasing the dissolved oxygen by HBOT has several beneficial effects in damaged brain tissues [17,18,19,20,21,22,23]. Recently, we reported that HBOT can induced neuroplasticity in post stroke patients even at chronic late stages, months-years after the acute event [23]. The mechanism by which HBOT is thought to improve the outcome of brain injury is multifaceted and includes different processes that have one thing in common – they are all energy/oxygen dependent[24].

Several studies revealed the beneficial effect of HBOT on the injured brain and cognitive function in animal models [25,26,27,28,29]. However, there are only few prospective clinical trials in TBI patients [30,31,32,33] and even fewer addressed the effect of HBOT on chronic mild TBI patients [30,34]. Harch et al. [30] presented a

pilot study in which HBOT was given to 16 subjects with chronic neurocognitive dysfunction due to mild to moderate TBI for 30 days. HBOT induced significant improvements in cognitive testing and brain metabolism as demonstrated by brain SPECT. The aim of our current study was to evaluate the effect of HBOT on cognitive impairments in chronic mTBI patients in a prospective, controlled, randomized, cross-over study.

## **METHODS**

The study was a prospective, randomized, controlled, cross over trial. The population included patients of age 18 years or older, who suffered from mild TBI (No or less than 30 minutes loss of consciousness), 1-6 years prior to their inclusion, and had subjective complaints regarding their cognitive function. Exclusions were based on dynamic neurologic improvement during the previous month; chest pathology incompatible with HBOT; inner ear disease; claustrophobia and inability to sign informed consent. Smoking was not allowed during the study. All patients signed written informed consent; the protocol was approved by the local Helsinki committee. The study was conducted in the hyperbaric institute and the research unit of Assaf-Harofeh Medical Center, Israel.

### ***Protocol and End Points***

After signing an informed consent form, the patients were invited for baseline evaluations. Included patients were randomized into two groups (1:1 randomization): a treated group and a cross over group. The neuropsychological function, evaluated by Mindstreams testing battery, was the primary endpoint of the study. Another primary end point was the evaluation of CBF and brain metabolism as visualized by SPECT. Secondary end point included quality of life evaluation by the EQ-5D questionnaire.

Evaluation was made by medical and neuropsychological practitioners who were blinded to patients' inclusion in the control-crossed or the treated groups. Patients in the treated group were evaluated twice – at baseline and after 2 months of HBOT. Patients in the cross over group were evaluated three times: baseline, after 2 months control period of no treatment, and after consequent 2 months of HBOT. The following HBOT protocol was practiced: 40 daily sessions, 5 days/week, 60 minutes each, 100% oxygen at 1.5ATA. Patients were not involved in any other cognitive or rehabilitation intervention as part of the study protocol.

### ***Neuropsychological evaluation***

Cognitive function was assessed using the Mindstreams Computerized Cognitive Test Battery (Mindstreams; NeuroTrax Corp., NY). Detailed description of the tests can be found on Neurotrax website ([www.neurotrax.com](http://www.neurotrax.com)). There are several cognitive tests in the battery, so only the most relevant for mild TBI were analyzed in this study. Following is a short description of the tests relevant for this study:

1. **Verbal memory:** Ten pairs of words are presented, followed by a recognition test in which the first word of a previously presented pair appears together with a list of four words from which the patients choose the other member of the pair. There are four immediate repetitions and one delayed repetition after 10 min.
2. **Non-verbal memory.** Eight pictures of simple geometric objects are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. There are four immediate repetitions and one delayed repetition after 10 min.

3. **Go–NoGo test.** Continuous performance test during which response of the patient is made to large colored squares that are any color but red.

4. **Stroop test.** Timed test of response inhibition modified from the paper-based test. In the first phase, participants choose the color of a general word. In the next phase (termed the Choice Reaction Time test), the task is to choose the color named by a word presented in white letter–color. In the final (Stroop interference) phase, participants choose the letter–color of a word that names a different color.

5. **Staged information processing test.** Timed test requiring a reaction (pressing right/left mouse button) based on the solution of simple arithmetic problems with three levels of information processing load, each containing three speed levels.

6. **Catch game.** A novel test of motor planning that require participants to catch a falling object by moving a paddle horizontally so that it can "catch" the falling object.

Mindstreams data is being uploaded to the NeuroTrax central server. Outcome parameters are calculated using custom software blind to diagnosis or testing site. To minimize differences in age and education, each outcome parameter is normalized and fit to an IQ-like scale (mean=100, S.D.=15) according to patient's age and education. Normative data consisted of test data of cognitively healthy individuals in controlled research studies at more than 10 clinical sites. A specified guide to the normative data evaluation and calculation can be found in Neurotrax's website.

Normalized subsets of outcome parameters are aggregated to produce six index scores, four of which, relevant to mTBI, were analyzed in our study: **Memory** index presents the mean accuracies for total learning score and delayed recognition phase of verbal and non-verbal memory tests, **Attention** index presents mean reaction time for Go–NoGo and choice reaction time (Stroop, second phase) tests, mean standard deviation of reaction time for Go–NoGo test, mean reaction time for a low-

load stage of staged information processing test and mean accuracy for a medium-load stage of information processing test. **Executive function** index is a performance index for Stroop test and Go–NoGo test, mean weighted accuracy for catch game. **Information processing speed** index is the composite score for various low and medium-load stages of staged information processing test. Construct validity of the tests and derived indices has been demonstrated in several cohorts, in comparison to paper-based, familiar and well established neuropsychological tests [35,36,37]. Three different tests versions exist in the Mindstreams test battery to allow repeated administrations, test-retest reliability for those versions was evaluated and found high, with no significant learning effect [38,39].

#### **SPECT part.**

#### ***Quality of life evaluation***

Quality of life was evaluated by the EQ-5D questionnaire [40]. EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system covers mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale [range: 0(worst)-100(best)].

#### ***Statistical analysis***

The statistical analysis was done using SPSS software (version 16.0). Continuous data is expressed as means  $\pm$  standard deviations and compared by one-tailed paired t-test for intra-group comparisons and two-tailed unpaired t-test for inter-group comparisons. Categorical data is expressed in numbers and percentages and compared by  $\chi^2$  test. P

values $<0.05$  were considered statistically significant. All randomly allocated patients were included in the safety analysis and those with complete post-baseline assessment were included in efficacy analyses.

## **RESULTS**

The study included 90 patients who were screened and signed an informed consent. Nineteen patients had their consent withdrawn before the beginning of the control/treatment period (13 in the cross over group, 6 in the treatment group); four patients decided to drop out during the treatment protocol, 3 due to personal reasons and one due to ear condition (1 in cross over group, 3 in treatment group). Seven patients (5 in cross over group, 2 in treatment group) were excluded due to technical performance problem in their cognitive test and 4 patients due to inconsistent use of medications (such as methylphenidate) during the tests period (2 in cross over group, 2 in treatment group). Accordingly, 56 patients (32 in the treatment group and 24 in cross over group) were included in the final analysis (figure 1). Twenty four (43%) patients were males, the mean age was 44 years (range of 21-66 years) and the average time from the acute traumatic event was 2.75 years. The most frequent etiology of the TBI was of vehicle accident (n=38), with some other less common etiologies (falls=7, object hit=6, pedestrian accident=3, assault=2). Baseline patients' characteristics are summarized in table 1; there was no significant difference in those measures between the groups except for in years of education, where the treatment group had a slight advantage.

### *Cognitive scores*

Cognitive scores are summarized in table 2. Baseline cognitive scores of all tests were similar for both treatment and control group. Following HBOT, as summarized in



table 2 and figures 1.1-1.4., a significant improvement in all cognitive measures was observed in treatment group: Memory ( $t_{(31)}=4.13$ ,  $p<0.0005$ ), Executive function ( $t_{(31)}=3.72$ ,  $p<0.0005$ ), Attention ( $t_{(31)}=3.26$ ,  $p<0.005$ ) and Information processing speed ( $t_{(31)}=4.20$ ,  $p<0.0001$ ). No significant improvement was noticed in the crossed group during the control period: Memory ( $t_{(23)}=0.74$ ,  $p=0.233$ ), Executive function ( $t_{(23)}=0.54$ ,  $p=0.295$ ), Attention ( $t_{(23)}=0.33$ ,  $p=0.368$ ) and Information processing speed ( $t_{(23)}=0.53$ ,  $p=0.298$ ). However, as in the treatment group, a significant improvement was notice in the crossed group following HBOT: Memory ( $t_{(23)}=3.21$ ,  $p<0.005$ ), Executive function ( $t_{(23)}=2.26$ ,  $p<0.05$ ), Attention ( $t_{(23)}=2.29$ ,  $p<0.05$ ) and Information processing speed ( $t_{(23)}=1.98$ ,  $p<0.05$ ).

## **SPECT**

### *Quality of life*

The effect on the quality of life is summarized in Table 2. The EQ-5D score significantly improved following HBOT in the treated group ( $t_{(31)}=7.41$ ,  $p<0.0001$ ) and in the cross group after HBOT ( $t_{(23)}=6.17$ ,  $p<0.0001$ ). There was no improvement in the EQ-5D score in the control group following the control period. Moreover, in the control group during the control period significant deterioration was noticed with respect to the patients' subjective perception of their quality of life ( $t_{(23)}=2.60$ ,  $p<0.01$ ). Similar results were obtained for the EQ-VAS evaluations as summarized in Table 2. More specifically, the EQ-VAS score significantly improved following HBOT, both in the treated group ( $t_{(31)}=4.86$ ,  $p<0.0001$ ) and in the crossed group following treatment ( $t_{(23)}=4.79$ ,  $p<0.0001$ ), while there was no significant improvement following the control period ( $t_{(23)}=0.32$ ,  $p=0.373$ ).

Finally, a comparison of endpoint scores of all dependant measures in both groups was made; the effect of HBOT was similar in both treatment group and cross-over group after the cross to the HBOT (table 2).

## **DISCUSSION**

In this study, the effect of HBOT on patients suffering from chronic cognitive impairments due to mTBI was evaluated in a prospective, randomized, controlled, cross-over clinical trial. HBOT induced significant cognitive improvement, **improvement in brain perfusion** and improvement in quality of life compared to control. The most significant improvement was in the memory index score. Other cognitive measures, including executive function, information processing speed and attention had also been improved significantly following HBOT.

Patients with mTBI have more frequent and more extensive areas of abnormality as measured by functional/metabolic brain imaging (SPECT, PET, CT perfusion, and functional MRI) than can be seen on anatomical imaging (conventional CT and MRI scans), supporting a role for diffuse structural and/or physiologic/metabolic derangement in mTBI [41,42,43]. **SPECT results by Golan.**

The current acceptable treatments for mTBI patients, if any, focus on relieving the cognitive symptoms using different behavioral compensation methods, such as attention training drills, teaching memory and planning strategies, usage of external aids, etc. [44,45]. This approach, although common in rehabilitation processes, has its share of problems since it is dependant greatly on patient's health, awareness, motivation and compliance, as well as other psychosocial factors 46][. Most importantly, these approaches do not directly intervene or enhance metabolic mechanisms needed for the regenerative processes of the injured brain. HBOT, as **evident by brain SPECTs**, initiate neuroplasticity in the damaged metabolic

dysfunction brain tissue years after the acute event. The ability of HBOT to induced neuroplasticity in the late chronic phase was also notice in post stroke patients [23].The mechanism by which HBOT improves the outcome can be understood in matters of providing the oxygen/energy to different healing and regeneration processes, relevant to the primary and secondary injury mechanisms in mTBI: in matters of primary axonal injury, HBOT induced regenartion of axonal white matter [47,48,49,50], HBOT has positive effect upon the myelinization and maturation of injured neural fibers [51], stimulation of axonal growth and increasing the ability of neurons to function and communicate with each other [52]. In addition, HBOT was found to have a role in initiation and/or facilitation of angiogenesis and cell proliferation processes needed for axonal regeneration [53]. As for brain contusions and direct brain cell injury, HBOT can also contribute to damaged cells through improvement of mitochondrial function (in both neurons and glial cells) and cellular metabolism. Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells, including astrocytes [21]. HBOT may promote neurogenesis of endogenous neural stem cells [22]. As for secondary injury mechanisms in mTBI, HBOT initiate vascular repair mechanism and improve cerebral vascular flow [54,55,56,57], improve blood brain barrier integrity and reduce inflammatory reactions [27] as well as brain edema [18,19,20,25,30,58].

Our cognitive testing results are consistent with recent findings of Harch et al. pilot study [30]. However, as opposed to their chosen cognitive tests, our cognitive index scores were specific and designed to represent known impaired cognitive domains in mild TBI. In addition, each index in the Mindstreams battery referred to more than one test-score, thus turning the index score to be more of a cognitive domain score and less test-dependant score. We also chose a fully computerized

testing battery, allowing the inclusion of more accurate measures such as reaction time and accuracy, and eliminating the bias effect of tests' administration and hand scoring. Last, our tests included the cognitive domain of information processing speed, known to be impaired in mild TBI patients, which was not directly addressed in Harch et al.'s pilot study. Thus, our findings added relevant and significant information to the demonstrated improvement in cognitive scores in their pilot study.

A major limitation of our study is the lack of a "placebo" control group. The issue of "how to handle the control group" was discussed by a multidisciplinary team including physicians specializing in hyperbaric medicine, physicists specializing in neuronal-glia interactions and the ethics committee. Patients can tell if pressure is increased or not, so the pressure must be increased also in the control group. The only way to administer "placebo" of HBOT is to bring the patients to the hyperbaric chamber and to increase the environmental pressure to an extent that the patients will feel it in their ears. The minimal pressure needed to gain such a feeling should be 1.3 ATM. Henry's law states: "the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the pressure of that gas in equilibrium with that liquid". Thus, hyperbaric environment significantly increases the dissolved oxygen pressure even if a person holding his breath [59]. Compressed air at 1.3 ATA increases the plasma oxygen tension by at least 50% and that is certainly notable. There are many case reports illustrating significant effects following small increase in air pressure [60,61,62]. Moreover, even a slight increase in partial pressure, such as, for example, to 1.05 ATM at altitude 402 m below sea level (the Dead Sea), can lead to noticeable physiological effects [63,64,65,66,67]. However, it should be kept in mind that oxygen is not a drug, and because it is metabolized mainly in the mitochondria, there is no simple dose-response curve. Since increasing the pressure

even without adding oxygen can also increase the dissolved oxygen partial pressure, the only way to maintain normal (placebo) levels of dissolved oxygen is to supply air with lower than normal level of oxygen, which we deemed unethical. To partially compensate for this inherent limitation, the patients in the cross group started with a two-month control period of no treatment, at the end of which they were crossed to two months of HBOT sessions. To gain better validity of the results, study measurable end points (cognitive function and SPECT analysis) were done by a blinded evaluation and evaluator: the cognitive function tests were done by a computerized validated method and the SPECT analysis was blind to patients' participation in treatment/cross group. Moreover, the consistency between the changes in the brain metabolism, as demonstrated by the SPECT, with the finding in the cognitive evaluation together with the improvement in quality of life provides, together with the fact that effect of HBOT was similar in both treatment group and the crossed group after the cross to the HBOT, important validation for the strength of the results.

One randomized, controlled trial in patients with mild TBI is available, in which a comparison of “sham” treatment of room-air inhalation at 1.3 ATA to HBOT at 2.4 ATA was made. In this study, both groups revealed significant improvement in cognitive symptoms and post traumatic stress disorder (PTSD) measures, and unfortunately the conclusion was that there was no effect for HBOT in these patients. However, several problems embedded in this study protocol. The first and the most important is that 1.3 ATA is not sham. In the current study we have used 1.5 ATA in the treatment group and, as discussed above, compressed air at 1.3 ATA increases the plasma oxygen tension by at least 50% so it is actually a dose effect [68]. Moreover, it might be possible that such a high level as 2.4 ATA is less effective than 1.5 ATA or other lower levels of pressure [68]. Further studies are needed to evaluate the

specific dose effect curve in post TBI patients. Moreover, the researchers' conclusions concerning the lack of effect of HBOT compared to sham were based solely on subjective report of patients regarding their symptoms. No objective outcomes, such as cognitive tests or brain imaging, were in use. The use of subjective rating of symptoms by patients was probably less sensitive to change, and might be a reason for lack of significant difference between the groups.

In conclusion, our prospective randomized controlled study suggests that HBOT may induced neuroplasticity and improve cognitive function in patients with chronic neurocognitive impairment due to mild TBI. Further studies of HBOT are needed in order to optimize the HBOT protocol and the best time for initiating the treatment for this unfortunate large scale population.

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Table 1. Baseline patients' characteristics.

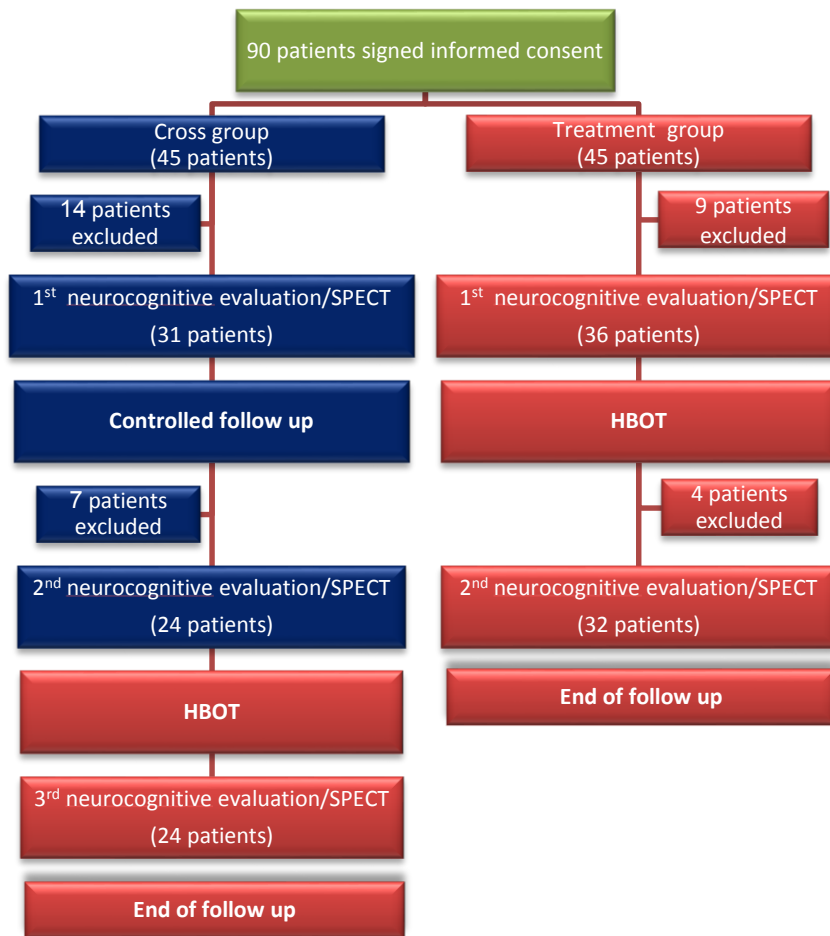
	<b>Treated group (n=32)</b>	<b>Cross group (n=24)</b>	<b>Comparison</b>
Age (years)	42.5 ±12.6	45.7±10.9	p=0.32
Gander - male	11 (34%)	13 (54%)	p=0.07
Years of education	16.2±3.9	14.0±3.1	p<0.05
Time since injury (months)	34.6±16.7	31.7±16.3	p=0.51
<b>Loss of consciousness</b>			
None	24 (75%)	14 (58%)	p=0.18
< 20 minutes	8 (25%)	10 (42%)	
<b>Etiology</b>			
Vehicle accident	20 (63%)	18 (75%)	
Fall	5 (16%)	2 (8%)	
Object hit	4 (12%)	2 (8%)	
Pedestrian accident	2 (6%)	1 (4%)	
Assault	1 (3%)	1 (4%)	
<b>Background disease</b>			
Hypertension (HTN)	5 (15%)	4 (16%)	
Diabetes Mellitus (DM)	2 (6%)	2 (8%)	
Hyperlipidemia	4 (12%)	3 (12%)	
Ischemic Heart Disease	0	1 (4%)	
Epileptic seizure	0	0	
Smoking	1 (3%)	0	
<b>Medications</b>			
Aspirin	2 (6%)	3 (12%)	
Glucose lowering drugs	2 (6%)	1 (4%)	
Anti-HTN	4 (12%)	3 (12%)	
Statin	3 (9%)	3 (12%)	
Anti-depressant	7 (22%)	4 (16%)	

**Table 2.** Summary of results of Mindstreams cognitive index scores, and quality of life questionnaire (EQ-5D and EQ-VAS). Values are presented as mean±SD.

P1=p values for baseline comparison of treatment and cross group. P2= p values for comparison of second measurement to baseline in the same group. P3 =p values of comparison of pre- and post-HBOT in the cross group .P4= p values for endpoint scores comparison following treatment in both groups.

	<b>Treatment (n=32)</b>		<b>cross over (n=24)</b>							
	<b>Baseline</b>	<b>HBOT</b>	<b>P1</b>	<b>P2</b>	<b>Baseline</b>	<b>Control-Pre HBOT</b>	<b>Post HBOT</b>	<b>P2</b>	<b>P3</b>	<b>P4</b>
Memory	82.43±25.15	96.54±17.18	0.567	<.0005	85.90±17.80	88.36±17.34	95.61±15.54	0.233	<0.005	0.835
Executive function	88.26±14.74	96.96±11.69	0.367	<0.0005	91.73±13.26	90.20±15.77	95.13±13.84	0.295	<0.05	0.595
Attention	85.13±20.28	95.30±12.90	0.854	<0.005	86.10±18.42	87.05±20.98	92.02±18.95	0.368	<0.05	0.443
Information processing speed	85.12±15.88	95.04±13.75	0.324	<0.0001	89.74±18.81	88.30±19.68	92.47±18.25	0.298	<0.05	0.55
EQ-5D	7.87±1.36	6.48±1.07	0.615	<0.0001	7.70±1.11	8.06±1.05	6.75±1.06	<0.01	<0.0001	0.362
EQ- VAS	5.03±2.31	6.62±2.45	0.696	<0.0001	5.26±1.70	5.21±1.66	6.39±1.80	0.373	<0.0001	0.696

**Figure 1. Flow chart of the patients in the study**



**Figure 2.1-2.4.** Mean scores+SE of cognitive tests (memory, executive function, attention and information processing speed, respectively) for (A) HBOT and cross group at baseline and following treatments; (B) Cross group at baseline, following waiting period, and following treatments.

