The Israeli Society for Hyperbaric Medicine & Diving (ISHMD)

Application of hyperbaric oxygen therapy in traumatic brain injury

Summary of Available Data and clinical Recommendations

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Content

Preface

The application of hyperbaric oxygen therapy (HBOT) for both acute and chronic traumatic brain injury (TBI) patients has been suggested over the past five decades. Nearly 50 years of pre-clinical and clinical research have passed with increased discussion and controversy. In the past decade, the design and quality of studies were more detailed leading to a better unerstanding understanding of the uses of HBOT. Currently, the level of evidence for the use of HBOT for persistant post concussion syndrome (PPCS) is stronger than any drug or therapeutic intervention use for that indicatio. Our purpose is to present a comprehensive literature review on the treatment for both acute and chronic TBI patients including the main strengths and limitations of each study. Considering the uptated available data, it is timely to reconsider the use of HBOT for chronic rather than in the acute setting for selected patients with PPCS.

Acute-subacute TBI: HBOT may be recommended in acute moderate-severe TBI patients (Type 2a recommendation, level A evidence) to reduce mortality. However, there are contradictory results (Type 2b recommandation, level A evidence) and further studies are needed to both evaluate outcomes and to determine the optimal treatment protocols for the different types of injuries (Type 1 recommandation, level A evidence). Myringotomy should be considered in all cases when there is no possibility for self-equilibration of pressure. (Type 3 recommendation, level C evidence).

Chronic TBI: HBOT should be recommended in chronic TBI (PPCS) for a selected group of patients who have clear evidence of metabolically dysfunctional brain regions (Type 2a recommendation, level B-R evidence). Patients who are candidates for HBOT should be properly evaluated prior to therapy by standardized cognitive tests and by functional imaging of the brain (Type 1 recommendation, level B-R evidence).

Background and epidemiology:

Traumatic brain injury (TBI) is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or projectile penetration. The major causes of TBI in high income countries are motor vehicle crashes (50%), falls (38%) and violence (including attempted suicide) (4%) (1). TBI has become a major public health concern worldwide for both civilian and military populations. At least 10 million new head injuries occur annually worldwide, and these account for a high rate of deaths in young adults (2). The annual incidence in the United States, for example, is estimated at 1.4 million people. Of these, 50,000 will not survive the acute injury, 235,000 will be hospitalized, and the remaining 1.1 million will be treated and discharged from emergency departments. Data are lacking on patients who have TBI evaluated in nonhospital settings or did not receive any medical care (3). These data do not include the military or veterans administration systems (4). In addition, patients whose TBI is secondary to sports-related injuries and do not seek medical attention may also add up to 3.8 million cases of unaccounted patients each year (5). TBI is noted to be the signature injury of the Afghanistan and Iraq military conflicts: 28% of the soldiers evacuated have TBI. There are no accurate statistics on mild TBI because most people don't go to a hospital, and 25% of those who do are never re-evaluated beyond the time of injury (6). According to the Center for Disease Control, more than 5 million Americans, or about 2% of the population, are living with long-term disabilities resulting from TBI (7, 8).

The health implications of TBI are multi-dimensional, dependent on the severity of TBI, and have a wide spectrum of physical, mental, social, and emotional disabilities. TBI also presents a considerable financial burden on individuals, families, national economies and health systems, with annual costs estimated at more than $56 billion (8).

Clinical presentation:

TBI classification is usually based on severity, anatomical features of the injury, and the cause of the injury. The severity is assessed according to the loss of consciousness (LOC) duration, the post-traumatic amnesia (PTA), and the Glasgow coma scale (GCS) grading of the level of consciousness.

About 70–90% of the TBI in the US are classified as mild TBI (mTBI) : LOC duration of 0–30 minutes, PTA duration of less than a day and GCS grade of 13–15 (9). Post-concussion syndrome (PCS) refers to a set of symptoms following mTBI.. The PCS syndrome includes headache, dizziness, neuropsychiatric symptoms (including behavioral and mood changes, confusion), difficulty balancing, fatigue, changes in sleep patterns and cognitive impairments (including memory, attention, concentration and executive functions disorders) (10, 11). PCS may continue for weeks or months, most patients recover but up to 25% of the patients may experience prolonged PCS (PPCS) in which the symptoms become chronic and last for over six months (12-15).

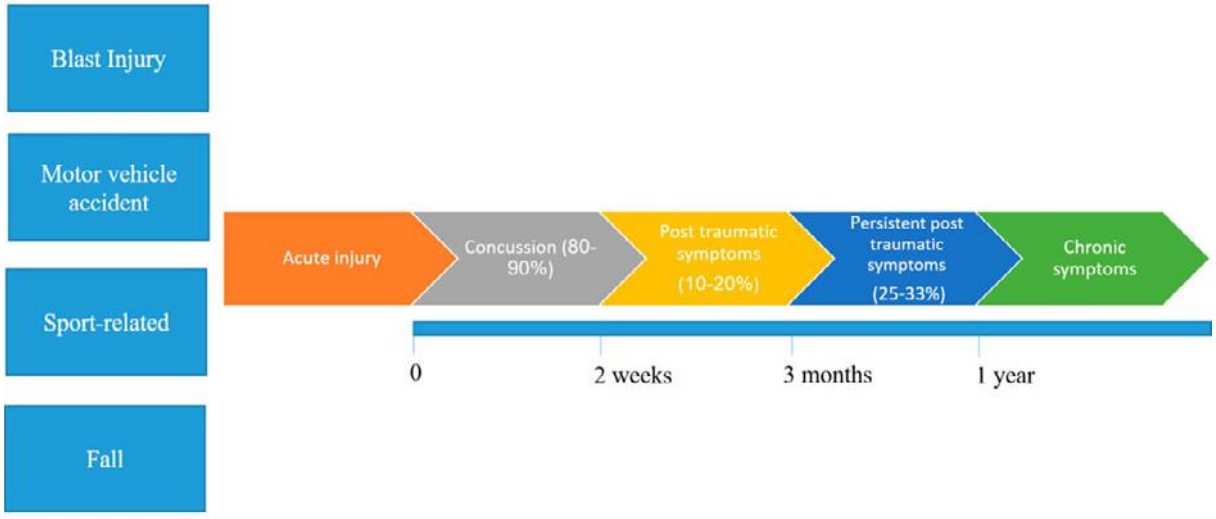

Figure 1: mTBI marching injury

The remaining 10-30% of TBI are classified as moderate to severe if one or more of the following criteria apply: death, loss of consciousness of 30 minutes or more, PTA of 24 hours or more, and the worst GCS full score in the first 24 hours is <13 provided that this is not invalidated by other factors such as intoxication or sedation. In addition if there is evidence of injury in neuroimaging, such as a hematoma, contusion or hemorrhage, the TBI would then be in the moderate-severe category (9). Patients with moderate-severe TBI may present with severe headaches, repeated vomiting or nausea, convulsions, variable levels of consciousness, anisocoria, dysphasia, dysarthria, weakness or numbness in the limbs, loss of coordination, confusion, restlessness, or agitation. The mortality rate in this group is up to 40% and survivors usually suffer from significant physical disability in addition to cognitive, psychological and emotional impairments (16).

Pathophysiology:

The pathophysiology of brain injury has primary and secondary components. At the time of impact the brain tissue may experience a variable degree of irreversible damage (primary injury). Primary injuries include contusions, lacerations, diffuse axonal shear injury, diffuse vascular injury and shearing of cranial nerves (17). Diffuse axonal injury is the hallmark lesion in TBI. The deceleration and acceleration forces most often associated with rotational forces cause axonal shear-strain, which results in cytoskeletal malalignment and permeability modifications. The shear-strain is more likely to develop in areas between tissues of different densities and viscosities. ***The microscopic extent of injury always exceeds the macroscopic abnormalities.*** The most frequent location of disruption is at the gray-white matter junction in the frontal and temporal lobes (18-20).

Following the primary injury, a chain of events may occur in which there is ongoing injury to the brain through edema, hypoxia and ischemia secondary to elevated intracranial pressure

(ICP), metabolic changes, infection, hydrocephalus, release of excitotoxic levels of excitatory neurotransmitters and impaired calcium homeostasis (21, 22).

Standard management and outcome

In the acute phase of TBI, therapy focuses on minimization of secondary injury by ensuring adequate oxygenation, hemodynamics, control of intracranial pressure, and strategies to reduce cellular injury (21, 22). Penetrating injuries or mass lesions such as intracranial hematomas are usually removed surgically. A number of therapies such as barbiturates, calcium channel blockers, mannitol, steroids, anti-convulsants, hyperventilation and hypothermia have been tried and none has shown unequivocal efficacy in improving prognosis (23-27). Moreover different centers use different treatment plans and there is suboptimal compliance with current evidence-based practice guidelines for moderate-to-severe TBI patients (28-30).

Currently, there is no effective treatment or metabolic intervention in daily clinical practice for post TBI patients with chronic neurological dysfunction. During the subacute-chronic phase, patients participate in intensive rehabilitation programs that aim to improve independent function and quality of life, mostly by helping the patients to adapt to their disabilities. Rehabilitation includes a multidisciplinary approach that may include physiotherapy, speech and language therapy, cognitive rehabilitation therapy, medications and others (31). However, several systematic reviews found limited evidence to support the efficacy of rehabilitation programs (32). Approximately 60% of severe TBI patients survive the acute injury. Out of those, 45-50% remain with moderate disability and 10% with severe disability. Many long term outcome studies concluded that patients with moderate-severe TBI show physical and functional improvement but remain with cognitive, emotional and neuropsychosocial impairments. These patients demonstrate significant limitations in daily living tasks (33-36).

As stated above, 25% of PCS patients develop chronic long-term disabilities (PPCS) (12-15). Patients treated for PCS receive various off-label pharmacologic and psychotherapeutic

interventions to address co-morbidities such as depression, but no medication has been approved by the united states food and drug administration (FDA) for treatment of any neuropsychiatric consequences of TBI (37). Rehabilitative therapies are selected to address symptoms persisting after injury, including physical visual and vestibular therapies. Patients are encouraged to participate in support groups to address cognitive symptoms (37).

Rationale for HBOT use

The brain receives 15% of the cardiac output, consumes 20% of the total body oxygen, and utilizes 25% of the total body glucose. At a standard healthy condition, the brain utilizes almost all the oxygen/energy delivered to it.

In the acute phase, hypoxia following TBI is an integral part of the secondary injury described above. The anaerobic metabolism utilized by hypoxic neurons results in acidosis and an unstable reduction in cellular metabolic reserve (38). As the hypoxic state continues, the neurons lose their ability to maintain ionic homeostasis and become prone to cell membrane degradation. Eventually, irreversible changes result in cell death (39). And even without cell death, metabolism is reduced in the hypoxic microenvironment and the decreased neuronal activity leads to loss of synapses and hampered neuronal connectivity (40).

HBOT can increase oxygen availability in the early period following TBI, reduce secondary injury and improve the long term outcome (41-45). Improved brain tissue oxygenation has been shown to improve aerobic metabolism and decrease brain lactate concentrations in animal models (46, 47) as well as in patients with severe TBI (48-50).

HBOT also improves cerebral vascular flow (48, 51-53), promotes blood-brain barrier integrity, preserves mitochondrial membrane properties (44), reduces inflammatory reactions (54), reduces both microgliosis and astrogliosis reactions (55, 56), decreases the lesion size (42, 44)

and brain edema, and reduces intracranial hypertension (42, 57, 58). HBOT may induce resilient mitochondrial transfer from astrocytes to inflammation susceptible neuronal cells (59). In the subacute-chronic delayed stage, previous animal studies have revealed the beneficial effect of HBOT on the chronically injured brain tissue and on the resultant cognitive dysfunction in animal models (43, 53, 60). The elevated oxygen concentration in the blood and injured tissue during treatment (47, 57, 61) can supply the energy needed for the process of neuroplasticity.

HBOT induces neuroplasticity by stimulating cell proliferation (62), promotes neurogenesis of endogenous neural stem cells (63), regenerates axonal white matter (64), improves maturation and myelination of injured neural fibers (65, 66), and stimulates axonal growth thus increasing the ability of neurons to function and communicate with each other (67, 68). At the cellular level, HBOT can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function (in both neurons and glial cells) (69 ,63 ,57). Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells, including astrocytes (70). The common denominator to all repair and regeneration mechanisms is that they are all oxygen dependent.

HBOT was also found to have a significant role in initiation and facilitation of angiogenesis, which is required for axonal regeneration (71-75). Local or diffuse hypoperfusion, as in TBI, is a limiting factor for any regenerative process (76-80). By inducing angiogenesis, HBOT improves the cerebral vascular blood flow necessary for neurogenesis and synaptogenesis (81, 82).

Evidence-Based review of HBO use

Acute and subacute TBI

There were 9 randomized controlled trials (RCT) (Holbach's 1974 article in German was not covered), one meta-analysis and two prospective study evaluating the clinical effects of HBOT in patients suffering from TBI in the acute and subacute settings. The studies had different HBOT protocols of time to treatment (several hours to 30 days), hyperbaric pressure (1.5-2.5ATA), dose of treatment (60 minutes daily to 3 sessions a day), number of sessions (3-42) and follow-up evaluation (days to 1.5 years). All RCTs compared a standard intensive treatment regimen to the same treatment regimen with the addition of HBOT. Only closed-head injuries were included.

The studies used mostly Glasgow coma scale (GCS) and Glasgow outcome scale (GOS) to evaluate the clinical effects. Several studies analyzed the scores as continuous parameters rather than nominal groups of favorable and unfavorable outcomes. In addition, several studies do not discuss the result per severity of injury at baseline.

Low level evidence:

Parkash's RCT (83) on 56 children (28 treated by HBOT) with severe TBI, treated 10 days post injury, reported significant improvement in GCS score (14 vs. 10 after 3 weeks). However, HBOT protocol was not revealed, GCS was referred to as a continuous parameter rather than nominal groups, and p-values were not supplied. These all considerably diminish the validity of this trial results.

Mitani's case series (84) reported some benefit depending on the type of brain injury: improvement in acute subdural hematomas and mild to moderate diffuse axonal injuries and poor outcomes in severe diffuse axonal injury. However, in addition to the retrospective nature of this data, the statistical analysis is lacking and the HBOT protocol is unclear.

Lee et al. case report (85) described a significant complication of HBOT in the acute trauma setting: tension pneumocephalus that mandated emergent surgery. Hence unrepaired skull base fractures and CSF leaks were suggested as contraindications.

Moderate/high level evidence:

The largest randomized controlled trial (RCT) in severe TBI patients, conducted by Rockswold (86), included 168 patients (84 treated by HBOT) and demonstrated a significant reduction in mortality rate (17% vs. 32%, p=0.037). Further analysis showed reduced mortality was mainly in patients with initial GCS of 4-6 (p=0.04) as well as patients with intracranial pressure higher than 20mmHg (p=0.02). It should be noted that intubated patients without myringotomy increased (rather than decreased) ICP during HBOT. Even though mortality was reduced, in those who survived there was no change in favorable clinical outcome. This trial had the most intensive protocol of HBOT, with 3 sessions of 60 minutes per day. In later studies done by the Rockswold group, the HBOT protocol was changed with significant reduction in the frequency/intensity of treatment. Myringotomy, which eliminated the ICP elevation during HBOT, was included in the treatment protocol.

In a later RCT (87), Rockswold focused on brain metabolism and oxygenation rather than the clinical effects in 69 patients (26 treated by HBOT) with severe acute TBI (87). The HBOT treated group had significantly increased tissue oxygenation ($p<0.003$), cerebral blood flow ($p<0.01$) and cerebral metabolic rate ($p<0.01$). The improved aerobic brain metabolism was reflected by decreased lactate and lactate/pyruvate ratio. The beneficial metabolic effects lasted 5-6 hours post HBOT session, while decreased intracranial pressure ($p<0.001$) was noticeable even 24 hours after the session. As stated earlier, this study did not evaluate any clinical status as primary or secondary outcome.

In a later RCT by Rockswold (88) that included 42 patients (22 treated by HBOT) with severe acute TBI, HBOT significantly decreased mortality by more than 50% (16% vs. 42%, p=0.04)

and increased the proportion of favorable outcome measured by GOS six months post injury in the HBOT treated group (74% vs. 38%, p=0.02). HBOT also decreased intracerebral pressure ($p<0.0006$), increased brain tissue oxygenation ($p<0.00001$) and improved aerobic metabolism with low lactate/pyruvate ratios ($p<0.0078$). In this trial, each HBOT session was followed by 3 hours of normobaric 100% oxygen treatment.

Ren's RCT (89) included 55 patients (35 treated by HBOT) suffering from acute TBI. The results clearly demonstrated statistically significant improvement in GCS score (5.1 to 14.6, $p<0.01$) as well as significant improvement in unfavorable outcome measured by GOS within 6 months post injury ($p<0.01$). There was also a significant reduction in abnormal brain activity ($p<0.01$), improved brain perfusion and decreased cerebral vascular resistance ($p<0.01$) (90). It should be noted that GCS was used as a continuous parameter and mortality cases were excluded from the study.

RCT by Mao et al. (91) included 60 patients with acute TBI (30 treated by HBOT). The results of the study demonstrated significant improvement in both GCS (P=0.05) and GOS (P=0.01) at 30 and 90 days post treatment. It should be noted that scores were referred as continuous parameters instead of nominal groups.

Lin et al. randomized (92) 44 patients within 22-32 days from injury (subacute TBI), where the HBOT group (22 patients) achieved statistically significant better GCS scores than the control group 3 and 6 months after treatment ($p<0.05$). Statistically significant improvement was recorded for patients with GOS=4 at baseline ($p<0.05$). No significant differences were noticed between most severely injured groups of patients, stratified to GOS 2-3. It should be noted that the study lacks analysis of outcome per severity of TBI and nominal groups of GCS instead of a continuous parameter.

Xie et al.'s RCT (93) included 60 patients with acute TBI (30 treated by HBOT). The study results demonstrated statistically significant improvement in GCS score with relation to standard neurosurgical care ($P < 0.01$). It should be noted that GCS scores were used as continuous parameters inadequately and there was no analysis of severity of TBI.

RCT in the late 70's by Artu (94) included 60 coma patients with acute TBI (31 treated by HBOT). While overall mortality and mean duration of coma were not changed by HBOT, further analysis revealed that the subgroup of young patients with brain stem contusions had statistically significant higher rates of recovered consciousness at 1 month ($p<0.03$). The main drawback in the study was the HBOT protocol which was inconsistent.

Meta-analysis done at 2012 (95) pooled 7 randomized controlled trials (not including the 2013 Rockswold's RCT mentioned above) and concluded that HBOT resulted in significant reduction of mortality, preventing 1 death for every 7 patients treated (CI 4-22), and GCS improvement of 2.68 ($p<0.0001$). However, no significant improved functional outcome was reported in those who survived even though a clear trend was demonstrated ($p=0.07$). It should be noted that those trials that did not assess functional outcome properly were excluded from that analysis. In addition, in several studies, GCS was referred to as a continuous parameter rather than nominal groups.

A prospective study done by Mogami (96) included 51 TBI patients and showed neurological improvements in 50% of the patients during hyperbaric exposure. 33% had remarkable improvement which included restoration of mental and neurological function. In addition, EEG abnormalities decreased in 33% of the patients. Cerebrospinal fluid pressure decreased considerably during treatment and reverted rapidly during decompression. No statistical analysis or severity of injury was given.

Zhong et al. (97) performed a prospective study on 88 severe TBI patients. Half of the patients were randomized for HBOT, started one week from admission, while the other half recived

standard care. The HBOT group had significantly better prognosis (34% with good prognosis compared to 14% in the control group). Additionally, the HBOT group had higher GCS, and lower NIHSS scores. The GCS score at admission, tracheotomy status, and first hyperbaric oxygen therapy timing were independent prognostic factors in patients with severe traumatic brain injury. The limitations of the study included variable timing and number of sessions. (Although there was not a true sham control group, its inclusion in the acute severe TBI scenario would be extremely challenging)

Lu et al. conducted a multicenter randomized controlled trial on 158 moderate-severe TBI patients treated with HBOT within the first 15 days of injury. The study indicated that an intesified program of 60 HBOT sessions of two sessions a day provided significant higher cognitive (Mini-Mental State Examination (MMSE), and neurological improvements (Fugl-Meyer Assessment, Functional Independence Measure, Modified Barthel Index) that was reflected by better quality of life at 1-3 months post injury compared to the control groups. The study used several controls including rehabilitation and one HBOT session a day, and rehabilitation without HBOT at all. However, no sham treatment was used. In addition, the HBOT protocol included 10 days break every 20 sessions, may have been improved.

Adverse events

No significant side effects were reported in all above mention studies during the acute-subacute phase of the injury. Two studies reported including patients with acute TBI reported that 13% of the patients had chest x-ray infiltrates. These chest infiltrates can be attributed to the acute setting of traumatic injury (chest injury or ventilator associated pneumonia in those who needed mechanical ventilation). Only one trial assessed CNS oxygen toxicity, which occurred in two (2.3%) of the patients and middle ear barotrauma was reported in two patients (2.3%) in one trial (95).

In summary, in the acute setting meta-analyzing the data is difficult due to the variety of treatment protocols and evaluation time points. However, HBOT in the acute-subacute setting after TBI improves both clinical and metabolic outcomes. Mortality was significantly reduced in all studies that used it as an end point. As for favorable functional outcomes, except for Rockwold's series with 3 daily sessions, all studies demonstrated significant improvement – most studies have shown more severely injured patients survived in the HBOT treated groups. One recent prospective study demonstrates a significantly better functional outcomes rates

It is clear HBOT has a beneficial effect on mortality, whereas the data on functional outcome is complex and the exact protocol to utilize remains undetermined. The HOBIT trial, funded by NINDS is ongoing and may shed additional light on the functional outcome and provide a determine acute protocol.

Due to the complexity of providing HBOT in the acute setting of severe TBI, we believe it should not be an approved indication at this time.

Chronic TBI:

There were 7 randomized controlled trials (RCT), 8 prospective studies and 4 cohort studies evaluating the clinical effects of HBOT in patients suffering from TBI in the chronic stage. The studies had different HBOT protocols for hyperbaric pressure (1.2-2.4ATA), severity of injury (mild-severe), number of sessions (40-120) as well as different methods of evaluation (PCS scales, PTSD scales, cognitive scores, SPECT and others). All RCTs showed that HBOT treated groups improved significantly compared to the pre-treatment score. The main issue in the RCTS is setting a proper control group. Low dose hyperbaric pressure (such as 1.3ATA) has significant physiological effects and therefore cannot and should not be considered as sham but rather as low dose treatment. It was demonstrated that low dosage (1.3 ATA), when used on the control group, had significant beneficial effects. A recent study demonstrated the effects of this protocol on cerebral blood flow. When a standard TBI treatment was compared to HBOT, the beneficial effect could be properly evaluated and clearly demonstrated both by clinical and bio-imaging end points. Since there is no standard for evaluation (such as GCS in the acute TBI), the studies used different measures of cognitive and neuropsychological evaluations which are hard to compare. Lastly, there's a clear need for objective patient selection using brain imaging and/or cognitive assessment rather than mTBI history alone.

Low level evidence:

Tal et al. evaluated 10 patients with PPCS due to mTBI in whom symptoms lasted more than 6 months since the acute injury (98). Significant improvement in cognitive functions (p=0.007) was demonstrated using computerized evaluation. Perfusion MRI showed significantly increased cerebral blood flow and cerebral blood volume. Study limitations: a relatively small sample and lack of control group.

Sanhi et al. performed retrospective analysis (99) of 40 patients (20 treated by HBOT) of which some were subacute and some chronic severe TBI cases. A significantly higher improvement in cognitive functions measured by Ranchos Los Amigos scale (RLAS) (50% vs. 25%) was noticed in the HBOT treated group. HBOT treated patients who were in a vegetative state had the highest improvement in disability rating scale (DRS) (40% vs. 20%). Patients treated within 1-6 months post injury had the highest proportion of recovery. Study limitations: in addition to the retrospective analysis nature of this study, the inclusion criteria were unclear, grouping of patients in final scores and p-values were not reported.

Churchill published a prospective study (100) that included 28 patients suffering from severe TBI for at least 1 year. Even though a year or more had elapsed since the acute insult, HBOT induced improvement in symptoms (51% memory, 51% attention/concentration, 48% balance/coordination, 45% endurance, 20% sleep). However, on standardized evaluations of cognition and questionnaires no significant changes were reported. A small subset of the patients had brain imaging, and of those more than 50% showed significant improvements in brain perfusion. The study has several limitations due to the small sample size, vague inclusion criteria and no control group. In addition, the statistics were calculated for the entire group of chronic brain injury and not specifically for post TBI patients.

Shi et al. (101) prospectively evaluated 310 patients with PCS or epilepsy and a history of trauma at least 1 month prior to inclusion. Post HBOT brain SPECT showed normalization of 50% of the perfusion defects. 70% of the patients had significant improvement in clinical symptoms. This is the second largest cohort reported that encourages the use of HBOT. However, it has several methodological flaws. 1) The inclusion criteria were vague, and the inclusion of seizures impairs the validity of the results as seizures are usually caused by more severe degrees of trauma. 2) The severity of trauma was not considered as epilepsy is usually caused by more severe degrees of trauma. 3) The statistical analysis was not satisfactory.4) There was no control group. 5) The clinical improvement was not well validated.

Harch et al. reported a case series (102) of 16 patients with military background and mild-moderate TBI for more than 1 year prior to injury. 80% of the patients reported improvement whereas all the patients had improved physical examination. In addition, there was a statistically significant improvement in the cognitive functions tests: IQ ($p<0.001$), working memory ($p=0.003$), Stroop test ($p<0.001$), memory ($p=0.02$), TOVA impulsivity ($p=0.04$). The patients had a significant improvement in psychological scores: PTSD ($p<0.001$), Rivermead PCSQ ($p=0.0002$), anxiety ($p=0.007$), depression ($p<0.001$). There was a significant Improved quality of life ($p=0.003$). Brain metabolism was evaluated by SPECT and increased perfusion/activity in white matter and several gray matter areas ($p<0.01$) was demonstrated. The use of imaging alongside cognitive and psychological evaluations is valuable in demonstrating the neuroplasticity effect of HBOT. The study was designed as a pilot study, and as such had obvious limitations of small sample size, lack of control group and the mix of few moderate TBI with mild TBI patients. In addition, the use of Rivermead PCS scale is problematic as discussed above. Half of the patients were active military servicemen and might have been biased due to potential secondary gain from reporting illness (gaining compensation). Nevertheless, this is one of the few and important studies capable of showing an improvement

in military service soldiers. In Israel this cohort of soldiers is not included in a prospective study due to ethical reasons (since soldiers are used to obey orders/request the validity of the informed consent is questionable) and possible secondary gain from reporting illness.

Ly LQ et al. series (103) included 6 patients who suffered from paroxysmal sympathetic hyperactivity after severe TBI unresponsive to accepted measures. Symptoms improved after HBOT. Since this is only a small size case series with no control group the evidence level is relatively weak. Yet, it sets the perspective of additional physiological effects of HBOT.

Wright et al. reported on a case series (104) of 2 military servicemen with PCS induced 6 months prior to treatment. The patients reported improved symptoms, and their automated neuro-psychological assessment showed improvement up to pre-injury levels. As a case series of a very small sample, its evidence level is very low. Nevertheless, this is yet another one of the few reports of military men whose symptoms of chronic PPCS improved after HBOT.

Barrett KF performed a non-randomized prospective study (105) on 10 patients who had suffered trauma 3 years prior to inclusion. The study did not find significant objective changes in neurologic and neuropsychometric tests nor any consistent pattern of perfusion changes over time in SPECT. The limitations of this study are the sample size and vague inclusion criteria.

Harch reported (106) on a military service veteran with chronic PCS and PTSD who experienced improved clinical symptoms and brain perfusion in bilateral frontal and temporal areas.

Hardy reported (107) on a patient with neurological symptoms due to injury 1 year earlier. After HBOT, there were improvements in both sensorimotor and neuropsychological symptoms, and EEG showed enhanced P300 amplitude in the damaged area. A year after treatment the patient symptoms relapsed, and after another series of HBOT sessions the improvements were reinstated. Despite being a case report it is worth noting as it suggests that some patients may

experience relapse and would benefit from additional therapy or a need for a longer duration of treatment. This is also the only report on EEG changes with HBOT used for PPCS patients.

Wooley et al. reported a case (108) of postural instability and walking difficulties due to severe TBI 2 years prior to intervention. Mild improvement was gained right after HBOT but was not evident 6 weeks later. The lack of anatomical and functional imaging may have been the key to failure in this case.

Neubauer et al. reported on a patient who suffered severe TBI 1 year prior to HBOT. Post HBOT, the patient had improved motor and cognitive functions as well as normalized perfusion in SPECT scans. The use of concurrent functional imaging strengthens the validity of the observed clinical effect. Notice that this patient received one of the largest number (188) of sessions in the literature.

A case report of a patient with chronic neurological deficits due to severe TBI by Lee et al. suggested that tension pneumocephalus is a rare complication that may occur in unrepaired skull base fractures (109).

Shandley et al. (110) included 28 mild to moderate TBI patients suffering from persistent cognitive impairment. They found a significant improvement in cognitive performance in (ImPACT, BrainCheckers and PCL-M) which correlated with stem cell mobilization. Unfortunately, no control group was evaluated.

Shytle et al. (111) reported on three patients with chronic TBI/PTSD symptoms (for 2-4 years) following mild TBI treated with 20-35 HBOT sessions at 1.5-1.75 ATA for 60 minutes with significant improvement in both cognitive profile and mood symptoms.

A case by Skiba et al. (112) reported on a severe TBI patient treated with 42 HBOT sessions, 1 year after his injury. Following treatment, patient improved his memory and concentration improved as well as his sleep, emotional lability and motor skills.

White et al. (113) reported on a severe TBI patient treated with over 165 HBOT sessions, combined with EEG based neurofeedback, with improved memory, executive function, language and seizures rate reduction.

Moderate level evidence:

Golden Z et al. prospective study (114) included 63 patients, of which 21 had chronic brain injury for more than 2 years. They were compared to 42 untreated, injured and normal patients. The study reported significant improvements in all neuropsychological parameters compared to the control ($p<0.0001$). The main limitations of this study were the vague inclusion criteria and definition of chronic brain injury, that not all patients had injury induced by clear TBI, and that the HBOT protocol was not clearly defined. It should be noted that the control group received more therapeutic interventions than usually applied in order to minimize the so-called placebo effect suggested by the DoD group.

Shi et al. RCT (115) had the largest cohort of patients with chronic TBI (320 patients, of which 195 were treated with HBOT). The study found significant difference in favor of the HBOT with relation to recovery from clinical symptoms, control of seizures, and resolution of hydrocephalus ($P<0.01$). Unfortunately, the study has vague inclusion criteria as well as insufficient statistical analysis.

Hart et al. performed a systemic review (116) of all four the DoD studies (see above) including 254 TBI patients. The pooled analyses indicated trends toward improveent in the subjective questionnares (Rivermead Total Score: -2.3, 95% CI [-5.6, 1.0], $p=0.18$); and verbal memory (CVLT-II Trial 1-5 Free Recall: 3.8; 95% CI [1.0, 6.7], $p=0.01$). A dose-response trend to increasing oxygen partial pressure was also found.

Hadanny et al. (117) analyzed the largest cohort of 154 chronic TBI patients of all severities treated with HBOT. HBOT was associated with significant improvement in all of the cognitive

domains, with a mean change in global cognitive scores of 4.6±8.5 ($p<0.00001$). The most prominent improvements were in memory index and attention. Significant improvement were observed in all TBI severities. Cognitive function changes correlated with increased activity in relevant brain regions evaluated with SPECT.

Harch et al. (118) included 30 patients with either PCS or PCS and PTSD treated with HBOT for 40 sessions. They found significant improvement in symptoms, cognitive domains including memory, measures of attention, dominant hand motor speed and dexterity in addition to quality of life, general anxiety, PTSD and depression symptoms which lasted 6 months post treatments. There was normalization of abnormal brain SPECT scans in 75% of the patients. The study has several limitations including a mixed population of active military men and veterans, with and without PTSD comorbidity and utilized an abnormal HBO protocol including two daily sessions.

Mozayeni et al. (119) evaluated 32 mTBI patients who suffered from chronic PCS with or without PTSD symptoms, treated with HBOT in 5 different centers. There were significant improvements in 13 out of 17 objective neurocognitive test components. Earlier administration of hyperbaric oxygen post injury, younger age at the time of injury and hyperbaric oxygen administration, military status, and increased number of hyperbaric oxygen administrations were characteristics associated with improved outcomes. The study was uncontrolled, had a mixed population, and treatment protocol was variable (monoplace/multiplace, 48-82 sessions).

Biggs et al. (120) evaluated the effect sizes of twelve previous studies. Across all studies, there was a robust and significantly different effect size in the treatment condition compared with the control condition. The average net symptomatic and cognitive effect sizes were medium at 0.57 and 0.40, respectively, after controlling for a placebo effect.

High level evidence:

Wolf's double-blind RCT on 50 military servicemen (121) suffering from mild TBI symptoms compared HBOT of 2.4 ATA to "sham" treatment of 1.3 ATA. Both groups showed considerable improvement in post-concussion symptoms and in the PTSD symptoms questionnaire ($p=0.001$). However, there were no differences between the groups ($p=0.35$ for self-reported PCS questionnaire and $p=0.84$ for PTSD questionnaire). Even though the study had a "sham" control group and double blinding was applied, it had several methodological pitfalls, and its equivocal interpretation of the findings calls for further discussion. First, the use of 1.3 ATA as sham treatment is a known dilemma in hyperbaric medicine. The only way to administer placebo pressure is to increase the environmental pressure to an extent that patients feel it in their ears. Alas, even at 1.3 ATA of compressed air there is a significant increase in plasma and tissue oxygen pressure by at least 50% (from 99mmHg to 147mmHg based on the alveolar air equation, taking into account water vapor and carbon dioxide are constants). It is well known that any slight increase in the partial pressure, even without changing the concentration it increase gas solubility (Henri's law), say 1.05 ATA (at the Dead Sea), can bring on significant physiological effects (122, 123). Abinder et al. report clear statistically signiciant increase in exercise duration and cardiac wall motion scores in cardiovascular disease patients($p<0.05$) (124). Thus, the evidence that both groups improved considerably beyond what would be expected 6 months or more after injury may be related of a non-sham treatment. 1.3 ATA may well serve as a low dosage effective treatment rather than sham control. The 2.4 ATA, based on what we know today is also not the optimal pressure to induce neuroplasticity due to inhibitory effects of very high oxygen levels in the tissues.

Furthermore, military patients introduce a major pitfall as this cohort has secondary gain in the form of financial compensation for their disability. The study was funded by the US department of Veterans Affairs (VA) and Department of Defense (DoD) and the patients were asked to

report about the symptoms by a self-assessment questionnaire. No objective end points such as metabolic imaging of the brain were used, and all conclusions were based on those questionnaires. With regards to the study cohort, the diagnosis criteria were based only on subjective reports and not on clear identification of biological brain damage, such as MRI/PET-CT or SPECT. Thus, patients with self-reported symptoms of PTSD could have been included without any direct injury at the brain tissue level.

In summary, the authors may have reached the wrong conclusions for the following reasons related to the methodology :

- Room air at 1.3Atm cannot serve as sham control but rather as low dosage of the treatment (124, 125).
- 100% oxygen at 2.4Atm is not the optimal dosage for induction of neuroplasticity since it can give rise to oxygen levels high enough to cause an inhibitory effect or even focal toxicity.
- The diagnostic criteria were not based on clear, direct demonstration of biological damage at the level of the brain tissue by brain imaging (MRI, PET-CT or SPECT).
- Soldiers may have secondary gain from reporting illness, which is a source of bias in a study whose end points are based only subjective self-assessment questions.

Cifu's RCT (126, 127), also funded by DoD-VA, was conducted on 61 active military servicemen with PCS symptoms for at least 3 months. They were divided into 3 groups with different FiO2 (75%, 100%, 10.5%) at 2 ATA. The study did not find any major significant differences between the groups, accept for several items in group 2 and group 3, with regards cognitive functions, RPQ questionnaire or eye-movements ($p>0.05$ for all measures) between the groups. Cifu's study may have been double blinded, but its many drawbacks, similar to those of the study by Wolf et al., render it quite unsuitable as a source of consistent, meaningful

information based on what we know today with regards to the use of HBOT for induction of neurplasticity. In addition to the above-mentioned ones (secondary benefit from reporting illness, lack of objective measures of brain damage, and non-neutral "sham") it should be noted that the soldiers included were treated with high doses of multiple psychiatric drugs, much more than usually expected in civilians suffering from PPCS (drugs that were not proved to have any beneficial effect in PTSD). With regards to the study end points, the use of Rivermead post-concussion symptoms questionnaire has several flaws in implementation as well as in reflecting the severity of the PCS. In addition, because many of the cognitive tests performed do not have a second version for retaking (such as WAIS), a learning effect would have been expected in the post treatment evaluation, making these endpoints unsuitable for such a study. In addition, as in the previous study, co-morbidities such as PTSD or depression were not excluded so it is not a clear PCS study.

Miller et al. RCT (128), funded by the DoD-Va, included 72 active military servicemen with PCS from mTBI more than 4 months prior to inclusion, divided into 3 groups: HBOT at 1.5 ATA, "sham" (low pressure) of 1.2 ATA breathing air, and a standard TBI care group. The study reported significant improvements in both HBOT and sham groups in post-concussion symptoms and neuropsychological symptoms (p=0.008 in HBOT and 0.02 in "sham") and no improvement in the TBI care group. Actually, The TBI care group showed worsening compared to the so called "sham" and HBOT groups. However, there were no significant differences between the HBOT and "sham which is actually low dosage group (p=0.7). This study re-confirms that any hyperbaric pressure above 1 ATA cannot serve as sham intervention. (As mentioned above, 1.2-1.3ATA of compressed air are not equivalent to normobaric hyperoxia). The authors, however, interpreted the findings as indicating that the chamber serves as a placebo effect inducer. It should be noted that the subgroups in this study were relatively small (22-24) for comparison between groups. In addition, as in the previous DoD-VA funded studies, the

subjects were (a) military men with obvious secondary gains; (b) relocated to a high-altitude site (Colorado according to methods and clinicaltrials.gov protocol). (c) The RPQ questionnaire with its methodological problematic issues was used as the primary outcome indicator and (d) no objective brain imaging were done not even as an inclusion criteria.

Boussi-Gross et al. RCT (129) included 56 patients, civilians, with PPCS 1-6 years after the acute insult in a crossover design protocol. The study used objective computerized cognitive tests with well validated different versions for reliable test-retest comparison. Patients' reports were clear from any secondary gain. The HBOT group showed significant improvements in all cognitive functions: memory ($p<0.0005$), executive functions ($p<0.0005$), attention ($p<0.005$), and information processing speed ($p<0.0001$). The control group had no significant change in any of the parameters ($p>0.2$). Then, when the control group was crossed to HBOT, they showed statistically significant cognitive improvements ($p<0.05$) similar to those of the HBOT group ($p>0.4$). The same pattern was seen in the quality of life score. The study included objective metabolic brain imaging of the brain (SPECT) that clearly demonstrated, abnormality at baseline and significant improvement of brain activity after HBOT. Moreover, the increased brain activity, demonstrated by the brain imaging, correlated with the cognitive improvement. This is the first RCT which had a control group that was not treated with a "low dosages sham". The crossover design afforded a triple comparison for proper evaluation of the net HBOT effect. The major limitation in this study was the selection of patients by their brain SPECT, which may not always be feasible for all, but is crucial for objective patient selection. The results of this study should guide the proper use of HBOT on selected PPCS due to mTBI that have a well defined metabolic brain injury.

Weaver et al. (130), funded by the DoD-Va, randomized 71 both active military servicemen and veterans who suffered from PCS more than 3 months to 5 years after mild TBI. Participants were divided into 2 groups: 40 daily HBOT sessions at 1.5 ATA or "sham" (low pressure) of

1.2 ATA breathing air, given in 12 weeks. In an intention to treat analysis, the HBOT group had significant improvements in their 13-week RPQ-3 and neurobehavioral symptoms inventory and single trait anger expression inventory scores compared to sham. In participants with PTSD, change with HBOT was more pronounced. Improvements regressed at six and 12 months. Patient Global Impression of Change showed significant improvemnt in HBOT (19/36) compared to the sham group (5/35) at 6 months. HBOT improved some cognitive processing speed (verbal learning, code substitution delayed and matching-to-sample throughputs) and sleep measures (Pittsburgh Sleep Quality Index). Participants with PTSD receiving HBOT had improved functional balance and reduced vestibular complaints at 13 weeks. Wetzel et al (131) reported the eyetracker measurements, which were abnormal at baseline for both groups, improved and normalized similarly in both HBOT and sham groups at 13 weeks and after 6 months from intervention. Although study design was significantly improved compared to previous DoD studies, (a) subjects were a mixed group of both active military men and veterans, which may have secondary gains. (b) although objective imaging was performed, it didn't serve as a method for patients' selection. (c) there were significant breaks of over 2-4 weeks in patietns' protocols, with 40 daily sessions given in 12 weeks rather than 8. (d) Intention to treat included over 6-7 patients (20%) which did not receive the designated protocol. (e) PTSD comorbidy was a significant cofactor. (f) As above, the control protocol of 1.2 ATA could not be regarded as a true sham,

Hart et al. (132) reported long term follow up on a small group (20%) which consented for an extended follow up. They did not find significant differences between the HBOT and sham groups, and noted group mean scores trended towards baseline values. However, the authors admit the results may be attributed to selection bias, participant or perception effects rather than a possible wanning effect of HBOT.

Meehan et al. (133) compared 71 military men who suffered mild TBI from the DoD studies treated with both HBOT and sham protocol to 75 healthy adults. They reported beneficial effects in postural control (sensory organization test) favoring HBOT over the control group. Most significnat effects were found in patients with affective symptoms - depression and anxiety. The study shares the limitations of its origin DoD studies including mixed and imbalanced populations, protocol assurance, mixed interventions, and comorbidties among others.

Similarly, Walker et al. (134) analyzed the sleep measures on the same 71 military men from the two DoD studies and compared to 75 healthy adults. Patients treated with HBOT had improved self-reports of the Pitssburg sleep quality infex (PSQI) in both 13 weeks and 6 months post sessions.

Ma et al. (135) evaluated low pressure HBOT protocol (20 sessions of 1.3 ATA for 45 minutes) in 14 firefighters suffering from chronic mTBI compared to 14 healthy controls. They reported a significant increase in cerebral blood flow in the limbic system, mainly the hippocampus and parahippocampal regions, as evaluated in perfusion MRI. The study confirms that low dose HBOT, that has been used as an inert “sham” treatment, has a significant biological effect. Unfortunately, the study does not offer clinical evaluations rather than the MRI. Additional limitations include the small sample size and absence of a sham treatment.

Harch et al. (136) RCT randomized 50 military and civilian patients suffering from PCS following mTBI to either 40 HBOT sessions at 1.5 ATA in 8 weeks or an equivalent no-treatment control period, which were then crossed-over for HBOT, similar to the design by Boussi-Gross et al. RCT (129). HBOT subjects experienced significant improvements in postconcussion and Post-Traumatic Stress Disorder symptoms, memory, cognitive functions,

depression, anxiety, sleep, and quality of life (Neurobehavioral Symptom Inventory, Memory Index, Automated Neuropsychological Assessment Metrics, Hamilton Depression Scale, Hamilton Anxiety Scale, Post-Traumatic Stress Disorder Checklist, Pittsburgh Sleep Quality Index). Improvements sustiated more than 3 months after the last HBOT session. After crossing over to HBOT, the Control Group experienced significant improvements similar to the HBOT group. The study is limited by its sample size, lack of objective based patients' selection and a sham control group.

Adverse events

Adverse events during the delayed chronic stage: Most studies did not report any significant side effects. In Harch study (102), there were 5/16 cases of mild reversible middle ear barotrauma, where 4 of them were due to upper respiratory infection. One patient experienced mild bronchospasm due to low-humidity oxygen in the monoplace. Churchill et al. (137) reported a rate of 1.1-2.2% of minor adverse events, with no serious adverse events in the two recent DoD studies.

Hadanny et al. (138) reported neurological patients (including TBI and PCS) had similar rate of adverse effects following HBOT (barotrauma and oxygen toxicity) as seen in non-neurological patients, with an overall per-session incidence of 721:100,000 events: sessions (0.72%).

In summary, meta-analyzing the data is complex due to the variety of treatment protocols and different methods of evaluation. There have been several RCTs but many of them had considerable methodological flaws. The few studies that were done with a proper control group, appropriate cohort without secondary gain and objective measurable

endpoints showed significant improvement in cognitive function, psychological aspects, quality of life, and brain metabolism.

Recommendations

Based on the currently available data, the following aspects should be address while selecting the appropriate patients and appropriate HBOT protocol:

- **Patient selection for HBOT**
  - ***Acute-subacute TBI:***

    Most studies in the acute-subacute settings evaluated moderate-severe TBI. Therefore, only moderate-severe TBI patients can be selected for HBOT in the acute-subacute setting (first day up to 1 month after injury). There is no evidence regarding the optimal time to HBOT. However, considering the pathophysiology of secondary injury, patients should be treated as soon as they are medically stable for treatment in a chamber. Currently, there is not enough evidence for the specific sub-types of injuries that can get the most gain from HBOT. The main exclusions which should be considered in these patients would be CSF leak and base of skull fractures, which may increase complications rate. Adequate on-site professional medical stuff and equipment is a must for proper care of ventilated patients within the hyperbaric chamber.

  - ***Chronic TBI:***

    Most of the studies in the chronic setting evaluated mild-severe TBI patients with PPCS, and HBOT started 6 months to several years post injury. The data in the 1-6 months period is lacking. Since mTBI can resolve in the first few months, it may be justified to withhold treatment in this period until PCS is considered PPCS.

The correlation of SPECT and clinical outcome promises better results and affords objective evaluation of the patients. Therefore, patients should have brain SPECT performed, and be selected for HBOT only if they demonstrate considerable metabolism defects.

- **HBOT protocol**
  - ***Acute TBI:***

    The best evidence for HBOT protocol in the acute-subacute settings was gleaned from Rockswold et al. The protocol was changed from 3 daily 60 minute sessions with 100% oxygen at 1.5 ATA to 1 daily 60 minute session of 100% at 1.5 ATA followed by 3 hours of normobaric oxygen with better outcome. The use of higher pressures, such as 2 ATA or 2.4 ATA, is less common and can't be shown to be preferable without direct comparison between the protocols. Until evidence shows otherwise, the protocol of choice should be the one easier to perform.

    Currently, there is not enough evidence regarding optimal number of sessions (3-25 sessions). In the authors' opinion, due to the complexity of transfers to the chamber, once daily session should serve as the standard and can be extended based on physicians' judgment according to the clinical progress, with a minimum of 3 daily sessions.

    Myringotomy should be performed in all patients in order to avoid ICP elevation during the treatment.

  - ***Chronic TBI:***

    Most evidence for HBOT in the chronic PPCS setting was gained with a protocol of 40-60 daily sessions most done with 1.5 ATA and there is accumulating data on the use of

HBOT at 2ATA, 100% oxygen for 90 minutes with 5 minutes air breaks every 20 minutes.

The optimal number of sessions for specific patients is not clear. 40-60 sessions were used in the different study protocols, and in the authors' opinion 40 daily sessions should be the minimum and 60 should be the recommended number for most patients, if feasible. Additional HBOT sessions can be considered based on the physician's decision per individual case.

It is highly recommended that all patients should undergo metabolic/ functional brain imaging such as brain SPECT evaluation before and after the treatment period. This may serve as an adjunctive tool for the decision whether of both eligibility and/or further continue of the treatment.

Cognitive evaluations should be standardized, with preference to automated objective evaluations. Tests should have several versions with high test-retest reliability.

Cost impact:

- ***Acute-subacute TBI:***

Financially: A previous cost-benefit analysis in TBI (139) showed that the medical and societal costs per patient depend on the GOS of the patient: GOS 4-5 adds up to $54,000, GOS 2-3 to $200,000, GOS 1 to $1,053,000.

The suggested protocol of a minimum of 3 treatments at 1.5 ATA for 60 minutes, depending on the special needs and complexity, would sum to $3,000-20,000. Compared to other medical interventions not proven in prospective clinical trials (surgery, hypothermia, Factor VII, and others) in the setting of acute TBI, this is one of the most cost-effective treatments that can be offered.

Medically: Based on the currently available data, 7 patients need to be treated in order to prevent 1 death. The reduced mortality is in addition to the clinical benefit for those who survive. HBOT is safe, with a complications rate of 2-3%. Since all acute TBI patients should have myringotomy performed prior to HBOT, the risk of sinus and ear barotrauma is basically non-existent. There is a risk for lungs barotrauma of ventilated patients with lung contusion.

Oxygen toxicity is considered very rare in any HBOT, especially when most patients with severe acute TBI are treated with preventive anti-epileptic drugs. Tension pneumocephalus is another possible rare complication that can be avoided by excluding patients with CSF leaks and skull base fractures.

- ***Chronic TBI:***

Financially: The cost per year of a patient with PPCS is about $32,000 (140). When considering a 40-60 sessions of HBOT, the total cost (not annual) would be $12,000-50,000, which is cost effective by all means. It should be noted that these numbers do not take into account the loss of work due to PCS and the return to work after HBOT of those who improve/recover with the treatment.

Medically: In a recent retrospective analysis, patients suffering from PCS did not have a higher complication rate compared to other HBOT patients. The usual risks of 40-60 sessions in HBOT are mild and reversible.

Conclusions:

Acute-subacute TBI: Based on the data available today, HBOT may be recommended in acute moderate-severe TBI patients (Type 2a recommendation, level A evidence) to reduce mortality.

However, there are contradictory results on functional outcome (Type 2b recommendation, level A evidence) and further studies are needed in order to both confirm outcomes and choosing the optimal treatment protocol for the different types of injuries (Type 1 recommendation, level A evidence). Myringotomy should be considered in all cases when there is no possibility for self-equilibration of pressure. (Type 3 recommendation, level C evidence).

Chronic TBI: Based on the data available today, low pressure HBOT should be recommended in chronic TBI (PPCS) for a selected group of patients who have clear evidence of metabolically dysfunctional brain regions (Type 2a recommendation, level B-R evidence). Patients who are candidates for HBOT should be properly evaluated prior to therapy by standardized cognitive tests and by a functional imaging of the brain (Type 1 recommendation, level B-R evidence).

It should be noted that the level of evidence for the use of HBOT for PPCS is higher than any drug or other therapeutic intervention (including psychotherapy, cognitive or behavioral intervention) currently used in those patients (summarized in Table 1).

Acknowledgement

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Table-1: Summary of the data available on the efficacy on the currently used therapeutics intervention for post-concussion syndrome

	Evidence level	Physical symptoms	Emotional symptoms	Cognitive symptoms
Cognitive behavioral therapy	Moderate	Mild improvement	Improvement	None
Cognitive rehabilitation	Weak	None	None	Mildly improvement in memory and attention
Education	Weak	Mild improvement	None	None
Exercise (subacute phase)	Weak	Improvement	Mild improvement	None
HBOT	Moderate-strong	Improvement	Improvement	Improvement
Mindful based stress reduction	Moderate	None	None	None
Pharmacotherapy	Weak and inconsistent	Improvement with anti-migraine drugs	Mild improvement with SSRI drugs	Mild improvement with SSRI, desmopressin and amantadine
Rehabilitation program	Moderate	None	None	None
Repetitive transcranial magnetic stimulation	Weak	None/Mild improvement	None	None/Mild improvement
Rest	Strong	None	None	None
Vestibular rehabilitation	Weak	Mild improvement	None	None
Spinal / Neck manipulation	Weak	Mild improvement	None	None
Oculomotor vision treatment	None/ Weak	Mild improvement	None	None
Immersive VR rehabilitation	Weak	None	None	None
Photobiomodulation	None	None	None	Mild improvement
Non-invasive brain stimulation (NIBS)	Moderate	None	None	None

Table-2: Class recommendations

Class recommendation	

1
(STRONG) Benefit >>> Risk
	• Is recommended
	• Is indicated/useful/effective/beneficial
	• Should be performed/administered/other
	• Comparative-Effectiveness Phrases†:
	  ○ Treatment/strategy A is recommended/indicated in preference to treatment B
	  ○ Treatment A should be chosen over treatment B

2a
(MODERATE) Benefit >> Risk
	• Is reasonable
	• Can be useful/effective/beneficial
	• Comparative-Effectiveness Phrases†:
	  ○ Treatment/strategy A is probably recommended/indicated in preference to treatment B
	  ○ It is reasonable to choose treatment A over treatment B

2b (WEAK) Benefit > Risk	• May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well established
3 (WEAK) Benefit = Risk	• Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
4 Harm (STRONG) Risk > Benefit	• Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other

Table-3: Evidence level

Level (quality) of Evidence	
A	• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies ○ over treatment B
B-R (randomized)	• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
B-NR (nonrandomized)	• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
C-LD (limited data)	• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
C-EO (expert opinion)	• Consensus of expert opinion based on clinical experience

Table-4: Evidence summary

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Lu 2021 (141)	RCT	158 patients (1) a control group receiving routine once-daily (1/d) rehabilitation training without HBO n=42 (2) study group A receiving routine 1/d rehabilitation training with HBO n=39 (3) study group B receiving twice-daily (2/d) intensified rehabilitation training with HBO, n=39 (4) study group C receiving 2/d intensified	Functional : Fugl-Meyer Assessment (FMA), Functional Independence Measure (FIM), Modified Barthel Index (MBI), Cognitive : and Mini-Mental State Examination (MMSE)	(1) TBI was confirmed by computed tomography (CT) or magnetic resonance imaging brain imaging, and the duration of TBI was less than 15 days, (2) GCS score ≤12 (severe form ≤8, moderate form 9–12), (3) age 18–70 years, and (4) no regular rehabilitation therapy before admission. Exclusion criteria were as follows: (1) history of motor and	HBO at 2.0 atmospheric pressure absolute (ATA) for 1 h daily for 20 days as a course of treatment for three courses, with a 10-day interval between every two courses.	FIM, FMA, MBI, and MMSE scores were improved significantly after 1-, 2-, and 3-month rehabilitation training in all TBI patients ($p < 0.01$), and this improvement was especially remarkable in patients who received 2/d intensified rehabilitation training with HBO ($p < 0.01$).	- No sham control - 10 days break between HBOT courses

		rehabilitation training without HBO n=38		cognitive dysfunctions (elicited from patient and/or family), (2) presence of severe major organ deterioration or failure, (3) being able to take care of daily life with a Modified Barthel Index (MBI) >70, (4) persistent coma >15 days, and (5) inability to obtain consent from patient or/and family.			
White 2021 (113)	Case report	1 patient	Clinical evaluation, cognitive evaluation	Severe TBI patient treated with HBOT and neurofeedback	165 HBOT sessions, combined with EEG based neurofeedback,	Improved memory, executive function, language and seizures rate reduction.	Case report Uncontrolled Large number of HBOT sessions
Biggs 2021 (120)	Retrospective / Systematic review	12 previous studies	Effect sizes of symptomatic effects, cognitive effects	Variable	Variable	There was a robust and significantly different effect size in the treatment condition	Statistical analysis of previous studies

						compared with the control condition. The average net symptomatic and cognitive effect sizes were medium at 0.57 and 0.40, respectively, after controlling for a placebo effect.	
Ma 2021 (135)	Prospective study	14 firefighters suffering from chronic mTBI, 14 healthy controls	Cerebral blood flow in Perfusion MRI	Firefighters who who suffered mTBI with chronic emotional symptoms	20 sessions of 1.3 ATA for 45 minutes)	significant increase in cerebral blood flow in the limbic system, mainly the hippocampus and parahippocampal regions, as evaluated in MRI perfusion.	No clinical evaluations No sham control Small sample size -
Skiba 2021 (112)	Case report	1 patient	Clinical evaluation Psychological evaluation Cognitive evaluation	Severe TBI patient treated with HBOT, 1 year after injury	Within 5 months, the patient underwent a series of 42 sessions each	Following treatment, patient improved his memory and concentration	Case report Uncontrolled

					of which lasted 90 minutes. During the first 3 weeks, there were sessions five times a week. Next, they were held three times a week for the next 4 weeks. The therapy was discontinued for 48 days because the patient needed to have his calvaria augmented. After the break, sessions were held three times a week for another 5 weeks.	improved as well as his sleep, emotional lability and motor skills.	
Harch 2020 (136)	RCT	52 military and civilian patients (HBOT n=25, Control n=27)	Neurobehavioral Symptom Inventory, Memory Index, Automated Neuropsychological Assessment Metrics, Hamilton	18–65 year old adults who had experienced one or more blunt or blast mTBIs, as	40 HBOT sessions at 1.5 ATA in 8 weeks or an equivalent no-treatment	Subjects experienced significant improvements in postconcussion and Post-	Sample size Lack of objective based patients' selection No sham control group

			Depression Scale, Hamilton Anxiety Scale, Post-Traumatic Stress Disorder Checklist, Pittsburgh Sleep Quality Index)	defined by the American Congress of Rehabilitation Medicine mTBI definition,52 that was at least 6 months old (3 months longer than the minimum time limit for definition of PPCS	control period, Control group was crossed over to HBOT.	Traumatic Stress Disorder symptoms, memory, cognitive functions, depression, anxiety, sleep, and quality of life (Neurobehavioral Symptom Inventory, Memory Index, Automated Neuropsychological Assessment Metrics, Hamilton Depression Scale, Hamilton Anxiety Scale, Post-Traumatic Stress Disorder Checklist, Pittsburgh Sleep Quality Index). Improvements sustiated more than 3 months after	

						the last HBOT session. After crossing over to HBOT, the Control Group experienced significant improvements similar to the HBOT group.	
Zhong 2020 (97)	Prospective	88 patients (44 HBOT, 44 control)	Glasgow coma scale, National institutes of health stroke scale (NIHSS)	Severe brain injury Glasgow Coma Scale (GCS) score between 3 and 8 points; Stable vital signs observed within 1 week after surgery with no active cranial bleeding as indicated by a computed tomography (CT) examination	1 week after admission when their vital signs had stabilized. 30 sessions, pressure of 0.20 to 0.25 MPa for 120 minutes	After treatment, an intergroup comparison revealed significantly higher GCS scores ($P < 0.05$) and significantly lower NIHSS scores in the experimental group relative to the control group ($P < 0.05$) The GCS score at admission, tracheotomy status, and first	Variable timing Variable number of sessions No Sham control group

						hyperbaric oxygen therapy timing were independent prognostic factors in patients with severe traumatic brain injury.	
Hart 2019 (116)	Meta Analysis	254 patients	PCS questionnares (Rivermead) , PTSD, and neuropsychological measures	18–65-year-old subject with a history of mild TBI a) with post-concussive symptoms or PTSD, b) a diagnosis of mild TBI with post-concussive symptoms and/or PTSD made by a neurologist or neuropsychologist, c) negative pregnancy test in females, and d) current symptoms or functional impairment attributable to	Planned for 40 sessions - Variable	Trends toward improveent in the subjective questionnares (Rivermead Total Score: -2.3, 95% CI [-5.6, 1.0], p=0.18); and verbal memory (CVLT-II Trial 1-5 Free Recall: 3.8; 95% CI [1.0, 6.7], p=0.01). A dose-response trend to increasing oxygen partial pressure was also found.	Military men Active sham treatment Variable protocols No patients selection

				TBI and/or PTSD.			
Mozayeni 2019 (119)	Prospective study	32 patients	"percent back to normal" assessment, the PHQ-15 (Patient Health Questionnaire-15), a measure of somatic symptoms associated with mental disorders, the PHQ-9 (Patient Health Questionnaire-9), a measure of depression symptoms, a quality of life assessment, and the Rivermead Post-concussion Symptoms Questionnaire Cognitive : Automated Neuropsychological Assessment Metrics (ANAM4^{TM}), Central Nervous System Vital Signs$^{®}$ (CNSVS)	18–65-year-old subject with a history of mild TBI a) with post-concussive symptoms or PTSD, b) a diagnosis of mild TBI with post-concussive symptoms and/or PTSD made by a neurologist or neuropsychologist, c) negative pregnancy test in females, and d) current symptoms or functional impairment attributable to TBI and/or PTSD. Exclusion criteria were: a) pulmonary disease that precludes HBO_2 administration, b) unstable		There were significant improvements in 13 out of 17 objective neurocognitive test components. Earlier administration of hyperbaric oxygen post injury, younger age at the time of injury and hyperbaric oxygen administration, military status, and increased number of hyperbaric oxygen administrations were characteristics associated with improved outcomes.	Uncontrolled Mixed population Variable treatment protocol

				medical conditions that are contraindicated in HBO_2 administration, c) severe confinement anxiety, d) pregnancy, d) a neurological diagnoses other than TBI or PCS, e) participation in another experimental trial with active intervention, f) high probability of inability to complete the experimental protocol, g) insufficient mental or physical capacity to complete the required tests, h) pre- or post-TBI history of systemic illness with impact on			

				central nervous system, i) pre-existing mental illness, and j) any pre-existing chronic infection not related to battlefield injuries or government service.			
Shytle 2019 (111)	Case series	3 patients	Mood scales, Cognitive scales	Chronic TBI/PTSD symptoms (for 2-4 years) following mild TBI treated with HBOT	20-30 sessions at 1.5-1.75 ATA, 60 minutes each	Significant improvement in both cognitive profile and mood symptoms.	Case series Uncontrolled
Meehan 2019 (133) Walker 2019 (134)	Retrospective analysis of RCTs	71 patients HBOT, 75 healthy controls	Balance and Gait Measures Sleep measures	Eligible active duty personnel or veterans were 18-65 years old with symptoms from ≥1 mild TBI. Consistent with post-concussive syndrome, ≥3 persistent symptoms were required	Daily one-hour sessions were provided Monday Friday in multiplace hyperbaric chambers at recruitment sites. Participants were to receive 40 HBO2	Significant between-intervention differences on balance measures were minimal but effects on postural control generally favored HBO2. Those with affective symptoms,	Mixed and imbalanced populations Protocol assurance Mixed interventions (HBOT/sham) Comorbidities

				for enrollment [13-15]. Exclusions included moderate/severe TBI, non-traumatic or penetrating brain injuries, or confounds of outcome measures or blinding. Participants were required to be stable on medications/ interventions for ≥30 days before enrollment	(>99% oxygen, 1.5 atmospheres absolute (ATA)) or sham (air, 1.2 ATA) sessions over 12 weeks to accommodate command and participant schedules	particularly PTSD, had the most improvement in postural control and otolith function following 13 weeks of HBO2. Patients treated with HBOT had improved self-reports of the Pitssburg sleep quality infex (PSQI) in both 13 weeks and 6 months post sessions. Other sleep measures were improved similary in both HBOT and sham treated patients.	
Weaver 2018 (130)	RCT	71 patients HBOT,n=36 Sham n=35	Symptoms, quality of life, and neuropsychological	Eligible active duty personnel or veterans	Daily one-hour sessions were	At baseline, 35 participants	Mixed group of both active military men and veterans No objective patients' selection

Wetzel 2019 (135) Hart 2019 (132)			testing. Questionnaires were self administered in private rooms, with study personnel available for questions. Neurological, electroencephalography, sleep, auditory/vestibular, electrocardiography, vision, neuroimaging, and laboratory measures	were 18-65 years old with symptoms from ≥1 mild TBI. Consistent with post-concussive syndrome, ≥3 persistent symptoms were required for enrollment [13-15]. Exclusions included moderate/severe TBI, non-traumatic or penetrating brain injuries, or confounds of outcome measures or blinding. Participants were required to be stable on medications/ interventions for ≥30 days before enrollment	provided MondayFriday in multiplace hyperbaric chambers at recruitment sites. Participants were to receive 40 HBO2 (>99% oxygen, 1.5 atmospheres absolute (ATA)) or sham (air, 1.2 ATA) sessions over 12 weeks to accommodate command and participant schedules	(49%) met post-traumatic stress disorder (PTSD) criteria. By the Neurobehavioral Symptom Inventory, the HBO2 group had improved 13-week scores (mean change -3.6 points, P=0.03) compared to sham (+3.9 points). In participants with PTSD, change with HBO2 was more pronounced (-8.6 vs. +4.8 points with sham, P=0.02). PTSD symptoms also improved in the HBO2 group, and more so in the subgroup	breaks of over 2-4 weeks in patietns' protocols, Intention to treat included over 6-7 patients (20%) which did not receive the designated protocol. PTSD comorbidy was a significant cofactor. Active sham control protocol of 1.2 ATA 20% long term followup

						with PTSD. Improvements regressed at six and 12 months. Hyperbaric oxygen improved some cognitive processing speed and sleep measures. Participants with PTSD receiving HBO2 had improved functional balance and reduced vestibular complaints at 13 weeks Consistent shifts of BIMA participant values toward Normal values at 13 weeks and six months were observed for overall	

						fixation duration, forward saccadic duration, and number of lines read for the reading task, number of misses on the memory guided-on task, and absolute intersaccadic interval velocity and absolute saccadic amplitude on the circular task. The distributions between Normal and BIMA participants were no longer statistically significantly different at 13 weeks and six months post enrollment for these measures.	

						Long term follow up on a small group (20%) which consented for an extended follow up, demonstrated no significant differences between the HBOT and sham groups, and noted group mean scores rended towards baseline values.	
Hadanny 2018 (117)	Retrospective	154 patients	Cognitive : Neurotrax	All patients suffering from TBI-related chronic neurocognitive damage (more than 3 months from injury), treated by HBOT and had pre and post cognitive assessments	40–70 daily hyperbaric sessions, 5 days a week. Each session consisted of 60/90 minutes of exposure to 100% oxygen at 1.5/2 ATA	HBOT was associated with significant improvement in all of the cognitive domains, with a mean	Retrospective No control group No long term evaluation Variable number of sessions

						change in global cognitive scores of 4.6±8.5 ($p<0.00001$). The most prominent improvements were in memory index and attention, with mean changes of 8.1±16.9 ($p<0.00001$) and 6.8±16.5 ($p<0.0001$),	

						respectively. The most striking changes observed in brain single photon emission computed tomography images were in the anterior cingulate and the postcentral cortex, in the prefrontal areas and in	

						the temporal areas	
Harch 2017 (118)	Prospective study	30 patients , 29 healthy controls for SPECT evaluation	Psychometric testing Wechsler Adult Intelligence Scale-IV Full Scale IQ (WAIS-IV), Wechsler Abbreviated Scale of Intelligence (WASI), Wechsler Memory Scale-IV Delayed Memory Index and Visual Working Memory Index (WMS-IV), Rivermead Post Concussion Symptom Questionnaire (RPCSQ), Test of Variables of Attention (TOVA), the Stroop Test, Finger Tapping and Grooved Pegboard Tests, the Paragraph memory subtest of the Rivermead Behavioural Memory Test, PTSD Checklist-Military (PCL-M), the Perceived	Active duty or retired military service men and women (18–65 years old) with one or more mild-to-moderate blast TBIS characterized by loss of consciousness that were a minimum of 1 year old and occurred after 9/11/01	100% oxygen to 152 kPa for 60 minutes total dive time, twice/day with a 3–4 hours surface interval, 5 days/week, for 40 sessions	significant improvement in symptoms, cognitive domains including memory, measures of attention, dominant hand motor speed and dexterity in addition to quality of life, general anxiety,	Mixed population of active military men and veterans. Comorbidities

			Quality of Life (PQOL), Generalized Anxiety Disorder Scale (GAD-7), the Patient's Health Questionnaire (PHQ-9), and the Percent Back To Normal Ratings (PBTN)			PTSD and depression symptoms which lasted 6 months post treatments. There was normalization of abnormal brain SPECT scans in 75% of the patients.	
Shandley 2017 (110)	Prospective	28 patients	Cognitive: ImPACT, BrainCheckers and PCL-M Peripheral blood stem cell count	Patients with persistent cognitive impairment caused by mild to moderate TBI suffered during military		Mild to moderate TBI patients suffering from persistent	Uncontrolled

				deployment to Iraq or Afghanistan		cognitive impairment. They found a significant improvement in cognitive performance in (ImPACT, BrainCheckers and PCL-M) which correlated with stem cell mobilization..	
Tal 2015 (98)	Case series	10 patients	Cognitive: Neurotrax computerized tests of memory, attention, executive function, information processing speed	Patients with mTBI for at least 6 months with who have completed two MRI brain imaging	60 min of 100% oxygen at 1.5 ATA X 60 sessions	<u>Outcome post treatment :</u> Significant improvement in the global cognitive scores with a mean change	Favors the use of HBOT in mTBI Small sample No control group

			including: verbal memory, non-verbal memory, go-no-go test, Stroop, staged information processing test, catch game. Brain imaging: Perfusion MRI			of 6.8±1.9 (p=0.007). The most prominent improvements were seen in information processing speed, visual spatial processing and motor skills indices, with mean changes of 9.6±2.9 (p=0.005), 10.1±4.2 (p=0.0043) and 9.5±4.5 (p=0.013) respectively. significant increased cerebral blood flow (CBF) and cerebral blood volume (CBV)	
Wolf 2012 (121)	Randomized controlled trial	50 patients	Psychologic: PTSD symptoms – Post traumatic disorder check list –military version (PCL-M) scores	Military service members with at least one combat-related mTBI	HBOT: 90 min of 100% oxygen at 2.4 ATA, 10 minutes air break every 30 minutes X	Within groups both HBO and Sham groups showed statistically significant improvement	No conclusion due to : Both groups improved more than would be expected greater than 6 months after mTBI. Selection of military service men as patients Secondary gain effect

			Cognition: Immediate post concussion assessment and cognitive testing (ImPACT)		30 sessions over 8 weeks Sham: 90 min of air (21% Oxygen) at 1.3 ATA X 30 sessions over 8 weeks	s in both PCL-M and ImPACT scores over the course of the study (p=0.001). No statistically significant differences between groups were noted, but both groups improved. Concussion history was critical for evaluation	1.3 ATA as placebo No exclusion of depression, PTSD or other comorbidities
Cifu 2014 (126)	Randomized controlled trial	60 patients (19 and 21 HBOT 21 Sham)	Eye movements in mTBI: saccadic and smooth pursuit parameters	Active Military service with post concussion symptoms for at least 3 months, injury within 3 years, at least 2 months of stable psychiatric status and no chance in psychiatric medications	Group 1: 60 min of 75% oxygen at 2 ATA X 40 sessions over 10 weeks Group 2: 60 min of 100% oxygen at 2 ATA X 40 sessions over 10 weeks Group 3 (Sham): 60 min of 10.5%	No statistically significant difference between the groups and no within groups differences (p>0.05 for all measures)	Relocation of patients for a high altitude naval base (NMOTC) Sham control with hypoxic levels of oxygen Selection of military service men as patients Secondary gain effect 2 ATA as Sham control No exclusion of depression, PTSD or other comorbidities

				for at least 1 months	oxygen at 2 ATA X 40 sessions over 10 weeks		
Cifu 2013(127)	Randomized controlled trial	61 patients (19 and 21 HBOT 21 Sham)	Post concussions symptoms: Rivermead post concussion symptom questionnaire (RPQ) Psychological: Post traumatic disorder checklist military version (PCL-M) and centers for epidemiological studies depression scale Cognition: Wechsler adult intelligence scale; Stroop; Trail decision making; continuous performance test; California verbal learning test; paced auditory serial addition test; Benton visual memory test; controlled oral word association test; Grooved peg board.	Active Military service with post concussion symptoms for at least 3 months, injury within 3 years, at least 2 months of stable psychiatric status and no chance in psychiatric medications for at least 1 months	Group 1: 60 min of 75% oxygen at 2 ATA X 40 sessions over 10 weeks Group 2: 60 min of 100% oxygen at 2 ATA X 40 sessions over 10 weeks Group 3 (Sham): 60min of 10.5% oxygen at 2 ATA X 40 sessions over 10 weeks	No significant time by intervention interaction was found for any functional, cognitive, or psychomotor secondary outcome. Statistically significant improvement in 2 items of RQP within group 2 ($p<0.05$). Other items without significance. Significant decrease in 2 items of PCL-M within group 3 (Sham) ($p=0.03$).	No conclusion due to : Relocation of patients for a high altitude naval base (NMOTC) Sham control with hypoxic levels of oxygen Selection of military service men as patients Secondary gain effect 2 ATA as Sham control No exclusion of depression, PTSD or other comorbidities

			Morbidity: Glasgow outcome scale extended (GOSE) And balance sensory organization test			Significant decrease in 1 item for group 1 (p=0.05). Significant decrease in 2 items as well as the total score in group 3 (p<0.05).	
Miller 2015 (128)	Randomized control trial	72 patients (23 Sham, 24 HBO + TBI care, 25 Sham +TBI care)	Post concussions symptoms: Rivermead post-concussion symptoms questionnaire-3 subscale (RPQ-3), Rivermead post-concussion symptoms questionnaire (RPQ), Neurobehaviroal symptom inventory scores (NSI) Cognition: automated neurophyschological assessment metrics (ANAM4 TBI-MIL) Psychological: PTSD checklist – civilian version (PCL-C), center for	Active Military service with at ongoing symptoms with 1 or more mTBI, latest at least within 4 months before randomization, stable medication for 30 days	HBOT: 60 min of 100% oxygen at 1.5 ATA X 40 sessions over 10 weeks Sham: 60 min of 21% oxygen at 1.2 ATA X 40 sessions over 10 weeks	No significant changes between groups in post concussive symptoms and cognition scores. However both groups undergoing supplemental chamber procedures showed improvement in symptoms : Within groups, Sham and HBOT groups had significant improvements in post concussion symptoms	No conclusion due to: Both HBOT and Sham improved more than real placebo group 1.2 ATA HBO as placebo No exclusion of depression, PTSD or other comorbidities Selection of military service men as patients Secondary gain effect

			epidemiologic studies depression scale (CES-D), Beck anxiety inventory (BAI), SF-36 mental health subscale			with ($p<0.04$) while TBI-care group did not improve. Within groups, both HBOT and Sham group had improved neurophysiological scores (p-values not published). PTSD and depression scores tended to favor sham vs. HBOT (p-values not published).	
Boussi-Gross 2013 (129)	Randomized controlled trial, crossover design	56 patients (32 HBOT, Control/Cross-over 24	Cognition: Neurotrax computerized tests of memory, attention, executive function, information processing speed including: verbal memory, non-verbal memory, go-no-go test, Stroop, staged	>18 years old patients who suffered mTBI 1-6 years prior to inclusion, at least 1 year of symptoms and no change in cognitive function in the last month	60 min sessions of 100% at 1.5 ATA oxygen X 40 sessions	Significant improvements were demonstrated in HBOT groups in all cognitive functions: memory ($p<0.0005$), executive function	Favors the use of HBOT in mTBI Randomized controlled trial with control group and crossover design Selection of patients with proper functional imaging

			information processing test, catch game. Quality of life: EQ-5D questionnaire and EQ-VAS Brain functional imaging: SPECT analyzed to calculate the mean perfusion in each broadmann area			(p<0.0005), attention (p<0.005) and information processing speed (p<0.0001). No significant improvement was observed following the control period (p>0.2). Significant improvement in cognitive function in the control group after treatment (p<0.05), with no significant difference from the HBOT group (p>0.4) Significant improvement in quality of life in both the HBOT group and the control group after being treated (p<0.0001)	

						SPECT imaging revealed elevated brain activity in good agreement with the cognitive improvemens.	
*Churchill 2012 (100)	Prospective study	28 patients	Neuropsychological measures, questionnaires, neurologic exams, physical functioning measures	Severe TBI at least 1 year prior to inclusion	60 min of 100% oxygen at 1.5 ATA X 60 sessions	Participants reported improvements in symptoms, such as memory and balance/ coordination. No standardized testing showed clinically important improvement.	No conclusion due to: Small sample size Vague inclusion criteria No control group
Rockswold 2013	Randomized controlled trial	42 patients (22 HBOT, 20 control)	Mortality Morbidity: Glasgow outcome score (GOS) Monitored variables: ICP,	Severe TBI (GCS<8) Or Mild-moderate TBI with deterioration to GCS<8 within 48	HBOT/NBH: 60 min of 100% oxygen at 1.5 ATA followed by 3 hours 100%	6 months post injury :26% reduced mortality (16% vs 42%, p=0.04) , 36% improvement	Favors HBOT use in acute TBI

			Microdyalisate Lactate/Pyruvate and glycerol, PbtO2, CSF F2-Isoprostane, BAL IL-6 and IL-8	hours from injury) CT scan grade >I	oxygen at 1 ATA X 3 sessions Control: standard care	in favorable outcome (74% vs 38%, p=0.02) Improved cerebral metabolism surrogates Decreased lactate, L/P ratio, ICP and increased PbtO2 within hours after treatment(P< 0.0001)	
Bennett 2012 (95)	Meta-analysis	571 patients (285 HBOT, 286 control)	Mortality Morbidity : GOS	Severe TBI	40-60 min of oxygen 100% at 1.5-2.5 ATA X 3-10 sessions	Significant decrease in proportion of unfavorable outcome (P=0.001). Significant decrease in mortality (p=0.003) Number needed to treat to prevent death =7	Favors HBOT use in acute severe TBI
Prakash 2012 (83)	Randomized controlled trial	56 patients – children (28 HBOT, 28 control)	Morbidity: Glasgow coma scale (GCS), disability, duration of hospitalization	Children with severe TBI (GCS<8)	Unknown time and pressure, 3 sessions at 1	Outcome at 3 weeks : Improved GCS,	Favors the use of HBOT in acute severe TBI Statistics unpublished

					week interval, 10-12 days after injury	decreased duration of hospitalization, decreased disability, improved social behavior (p-values were not published)	
Sahni 2012 (99)	Retrospective analysis	40 patients (20 HBOT, 20 control)	Morbidity: Disability rating scale (DRS, Glasgow coma scale (GCS), Ranchos Los Amigos Scale (RLAS)	severe TBI :No clear inclusion criteria – excluded if less than 30 sessions	60 min of 100% oxygen at 1.5 ATA X 30 sessions	Outcome at 1 month post treatment : Decrease in rate of vegetative and extremely vegetative states, decrease in DRS and RLA mean scores. Maximal improvements was seen in the group treated 1-6 months post injury (p-values not published)	Favors the use of HBOT in TBI Statistics unpublished
Harch 2012 (102)	Case series	16 patients	Symptoms: Rivermead PCS questionnaire, neurological exam	18-65 years old retired/active military	60 min of 100% oxygen at	80% reported on improved symptoms	No conclusion due to : No control group

			Psychological: PTSD symptoms by PCL-M, depression by PHQ-9, anxiety by GAD-7 Cognitive: Wechsler adult intelligence scale-IV, WMS memory tests, Stroop test, TOVA impulsivity, TOVA variability, grooved pegboard Quality of life: MPQoL, self report Brain imaging : SPECT	service , with post concussion symptoms due to mild-moderate TBI due to blast injury at least 1 year prior to inclusion	1.5 ATA X 40 sessions	100% had improved physical examination Significant improvement in cognitive functions IQ ($p<0.001$), working memory ($p=0.003$), Stroop test ($p<0.001$), memory ($p=0.02$), TOVA impulsivity ($p=0.04$). Significant improvement in psychological scores : PTSD ($p<0.001$), Rivermead PCSQ ($p=0.0002$), anxiety ($p=0.007$), depression ($p<0.001$) Improved quality of life ($p=0.003$)	Small sample Size Secondary gain of military subjects Rivermead PCS score

						Significant increases in mean perfusion in white matter and some gray matter ROIs	
Lee 2012 (109)	Case report	1 patient	none	15 months post severe TBI	unknown	Rare complication: tension pneumocephalus	Case report: patients with unrepaired skull base fracture and cerebrospinal fluid diversion be carefully evaluated before receiving hyperbaric oxygen therapy
Lv LQ 2011 (103)	Case series	6 patients	Paroxysmal sympathetic hyperactivity (PSH)	Paroxysmal sympathetic hyperactivity following extremely severe TBI	Non-published	Improved control of PSH changes (no statistics), after failure of standard care	No conclusion due to : Case report Small sample No control group
Rockswold 2010 (87)	Randomized controlled trial	69 patients: 26 HBO + standard care, 21 normobaric hyperoxia + standard care, 22 standard care	Brain tissue PO(2), microdialysis, and intracranial pressure Cerebral blood flow (CBF), arteriovenous differences in oxygen, cerebral metabolic rate of oxygen (CMRO2), CSF lactate and F2-isoprostane concentrations, and	Severe TBI (GCS<9)	90 min of 100% oxygen at 1.5 ATA X 3 sessions	Outcome within hours : ICP was significantly lower statistically after HBO2 until the next treatment session ($p < 0.001$) in comparison with levels in the control group	Favors the physiological effect of HBO in acute TBI

			bronchial alveolar lavage (BAL) fluid interleukin (IL)-8 and IL-6			Brain tissue PO2 levels were significantly increased in HBOT group and remained high until the next treatment session (p =0.003). HBOT significantly increased CBF and CMRO2 for 6 hours (p < or = 0.01). Microdialysis lactate /pyruvate (L/P) ratios were significantly decreased post-treatment HBOT group (p < 0.05)	
Mao 2010 (91)	Randomized controlled trial	60 patients (30 HBOT +standard treatment, 30	Morbidity: GCS, GOS EEG changes	Severe TBI (GCS<8) within 24 hours of injury	Unknown protocol, started 12	Outcome at 3 months post treatment :	Favors the use in acute TBI GCS as continuous parameters

		standard treatment)			days post injury	GCS at 20 d,30 d,90 d post treatment in HBO group were significantly increased (P=0. 05) score of GOS in HBO group was significantly higher than in control group (P=0. 01) Compared with control group, the scores of EEG at 30 d,90 d post treatment in HBO group were significantly decreased	
Wright 2009 (104)	Case report	2 patients	PCS symptoms Cognitive: Automated neuropsychological assessment metrics (ANAM)	Military service men with PCS induced by blast injury 6 months after injury	60 min of 100% oxygen at 1.5 ATA X unknown number of sessions	Improved symptoms (headaches and sleep) improved ANAM scores in all domains up to	Case report Small sample No control

						normalization of scores to pre-injury levels	
Harch 2009 (106)	Case report	1 patient	PCS symptoms PTSD symptoms, Brain imaging: SPECT	Military veteran with PCS and PTSD induced by blast injury 3 years earlier	60 min of 100% oxygen at 1.5 ATA for X 39 sessions	improvement in his post-concussive symptoms and PTSD symptoms improvements in brain blood flow at bilateral frontal and temporal defects	Case report Small sample
Lee 2009 (85)	Case report	1 patient	None	Acute severe TBI	unknown	Rare complication of tension pneumocephalus	Case report : Pneumocephalus, untreated skull base fracture, and CSF leakage may be considered contraindications to HBOT
Lin JW 2008 (92)	Randomized controlled trial	44 patients (22 HBOT, 22 control)	Morbidity: Glasgow coma scale (GCS), Glasgow outcome scale (GOS)	Moderate-severe subacute TBI, treated after an average of 22-32 days from injury	90 min of 100% oxygen at 2 ATA X 20 sessions	Outcome at 6 months post HBOT : HBO2 group achieved statistically significant better GCS scores than the control group post-intervention ($p<0.05$)	Favors HBO for subacute TBI No analysis per severity GCS as continuous parameter

						No significant differnces between groups stratified to GOS 2-3 at 3 & 6 months Statistically significant improvement between HBO group versus control in group stratified to GOS=4 at baseline ($p<0.05$)	
Xie 2007 (93)	Randomized controlled trial	60 patients (30 HBOT + neurosurgical care, 30 neurosurgical care)	Morbidity: Glasgow coma scale (GCS) C-Reactive-Protein	Acute TBI within the last 24 hours prior to inclusion GCS 3-12	80 min of 100% oxygen at 2-2.5 ATA X2-10 sessions	Post treatment : There was a statistically significant difference between HBO2 group and control group after treatment ($P < 0.01$).	Favors the use of HBO in acute TBI GCS as continuous parameters No analysis per severity
Hardy 2007 (107)	Case report	1 patient	EEG, metabolic and behavioral measurements	TBI 1 year prior 8to inclusion	60 min of 100% oxygen at 2 ATA for 20 sessions, and another 60	Improvements in sensorimotor functions and neuropsychological	Case report

					sessions 1 year later	improvements There was an enhanced P300 amplitude in the damaged hemisphere. Gains were no longer observed one year after treatment. However, after an additional treatment series of 60 exposures, the improvements were reinstated	
Shi XY 2006 (101)	Prospective study	310 patients	Brain imaging: SPECT, CT	History of trauma at least 1 month prior to inclusion and had PCS symptoms or epilepsy	90 minutes of 96% oxygen at 2 ATA X 20 sessions	Normalization of brain perfusion by 50% (from 81.3% to 29.7% abnormal areas). Improved symptoms (unknown proportion)	No conclusion due to : No control group Unknown clinical value

Golden Z 2006 (114)	Prospective study	63 patients (42 HBOT, 21 control)	Cognitive: Stroop, Luria-Nebraska neuropsychological battery, word fluency, logical memory	Chronic brain injury for at least 2 years	unknown	Significant gains in all neuropsychological areas compared to the control ($p<0.0001$)	Favors the use of HBOT in brain injury Unknown chronic brain injury source Unknown HBOT protocol Nonrandomized controlled
Barrett KF 2004 (105)	Nonrandomized prospective	5 HBOT, 5 head injury controls, 5 normal controls, 68 normal controls for SPECT controls	Cognitive: memory, mental tracking, attention, concentration, executive function, affect, motor. Specific tests: adaptive rate continuous performance, Wisconsin card sorting test, nonverbal intelligence-2, controlled oral word association, verbal selective reminding test, digit span. Behavioral: geriatric depression scale Symptoms: progressive exercise test Brain imaging: MRI, SPECT	TBI at least 3 years from injury	60 min of 100% oxygen at at 1.5 ATA X 80 sessions + another 40 sessions after 5 months break	No consistent change was seen in the neuropsychometric scores No consistent patterns of perfusion changes over time in SPECT Global depression scores were stable	No conclusion due to small sample
Mitani 2004 (84)	Case series	Unknown	Morbidity: Glasgow coma scale (GCS)	Acute severe TBI	Unknown	Outcome post treatment :	

						Improvements were observed in some acute subdural hematoma patients, yet the overall outcome was poor. Mild to moderate diffuse axonal injury patients recovered well. Poor outcomes in severe diffuse axonal injury	
Shi XY 2003 (115)	Randomized controlled trial	320 patients (195 HBO + medication, 125 medication only)	Symptoms Brain imaging: SPECT	Unknown	90 min of 96% oxygen at 2 ATA X 20-40 sessions	Significant difference in recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus (P<0.01).	Favors the use of HBO in TBI Unknown inclusion criteria
Ren H 2001 (89)	Randomized controlled trial	55 patients (35 HBOT + standard care,	Morbidity: Glasgow coma scale (GCS), Glasgow outcome scale (GOS)	Severe TBI (GCS<8)	40-60 min of 100% oxygen at 2.5 ATA X	Outcome at 6 months post treatment :	Favors HBO for acute TBI

		20 standard care)	Brain imaging: electric activity mapping (BEAM)		30-40 sessions	HBO2 group showed statistically significant improvement over control group ($p<0.01$) HBO2 group showed statistically significant improvement over control group at 6 months after injury ($p<0.001$)	
Woolley SM 1999 (108)	Case report	1 patient	Postural stability and walking	Severe TBI 2 years prior to study	60 min of 100% oxygen at 1.5 ATA, bi-daily X 40 sessions	Mild improvement immediately post treatment, This improvement was not evdient 6 weeks later	Disfavors the use of HBO in TBI : Case report
Neubauer RA 1994	Case report	1 patient	Motor evaluation, cognitive evaluation SPECT	Severe TBI 1 year prior to study	Unknown time of 100% oxygen at 1.5-1.75 ATA X 188 sessions	Improved motor and cognitive functions, normalized SPECT areas	Favors the use of HBO in TBI : Case report

Rockswold 1992 (86)	Randomized controlled trial	168 patients (84 HBOT +standard care, 82 standard care)	Mortality Morbidity: Glasgow coma scale (GCS), Glasgow outcome scale (GCS) Intracerebral pressure (ICP)	Severe TBI with GCS <10 for at least 6 hours	60 min of 100% oxygen at 1.5 ATA, three time daily average of 21 sessions	Outcome at 1.5 year : Mortality rate decreased to 17% compared to 32% in the control group (p = 0.037). Mortality in patients with an initial GCS score of 4-6 decreased to 17% compared to 42% in the control group (p=0.04) Mortality in patients with high ICP (>20mmHg) decreased to 21% compared to 48% in the control group (p=0.02)	Favors the use of HBO in acute TBI
Artru 1976 (94)	Randomized controlled trial	60 patients (31 HBOT, 29 standard care)	Mortality Morbidity: Glasgow outcome scale (GOS)	Severe TBI with COMA	60 min of 100% oxygen at 2.5 ATA X 10 daily sessions, followed by 4 days rest and repeat if	Outcome at 1 year: In a subgroup of young patients with brainstem injury, HBO2 group had statistically	Favors HBO use in some cases of acute TBI HBOT protocol was intermittent and inconsistent

					not responding	significant higher rates of recovered consciousness at 1 month ($p<0.03$)	
Mogami 1969 (96)	Prospective study	66 patients (51 TBI)	Symptoms EEG Cerebrospinal fluid pressure Lactate/Pyruvate levels	Severe acute cerebral damage	60 min of 100% oxygen 2 ATA + 6 sessions in 3 ATA	Outcome post treatment : Temporary neurological improvements were observed in 50% of the patients. 33% had remarkable degree of clinical improvement which included restoration of mental and neurological function reduction of EEG abnormalities was noted in 33% of the patients.	Favors the use of HBO in acute TBI No control group No statistical analysis

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