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RESEARCH ARTICLE

The Efficacy of Hyperbaric Oxygen Therapy in Traumatic Brain Injury Patients: Literature Review and Clinical Guidelines

Amir Hadanny[1], Joseph Maroon[3], Shai Efrati[1,2,4]

[1] Sagol Center for Hyperbaric Medicine and Research, Shamir (Assaf Harofeh) Medical Center, Zerifin, Israel
[2] Sackler School of Medicine, Tel- Aviv University, Tel-Aviv, Israel
[3] Neurosurgery department, UPMC, Pittsburgh, PA, United States
[4] Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel.

*Corresponding author: efratishai@outlook.com

ABSTRACT

Introduction: The application of hyperbaric oxygen therapy for patients with both acute and chronic traumatic brain injury has been suggested for over five decades. In the past decade, the design and quality of studies were more detailed and thorough leading to an improved unerstanding of the uses of HBOT and the profiles of the patients who can benefit the most.

Objectives: Perform a comprehensive literature review of hyperbaric oxygen therapy application for the treatment of patients with both acute, subacute and chronic traumatic brain injury.

Methods: Extensive literature search from 1969 to April 2023 was performed on April 1st 2023 within the following databases: Cochrane Library, PubMed, Google Scholar, and Web of Science, including humans clinical data, in articles providing information on the type of treatment and clinical outcomes. Articles were first categorized into acute-subacute traumatic brain inury and chronic traumatic brain injury and further classified into low, medium or high level quality.

Results: There was high level evidence including nine randomized controlled trials, one meta-analysis and two prospective study evaluating the clinical effects of hyperbaric oxygen therapy in patients suffering from traumatic brain injuries in the acute and subacute settings. Mortality was significantly reduced in all studies that used it as an endpoint, while favorable functional outcomes in survivors showed mixed results.

In chronic severe traumatic brain injury, there is low to moderate evidence including two uncontrolled prospective studies, two cohort studies and eight case reports suggesting improved outcomes.

In chronic mild traumatic brain injury, there is high level evidence including seven randomized controlled trials, and six prospective studies suggesting significant improvement in cognitive function, symptoms and quality of life.

Conclusions: Hyperbaric oxygen therapy may be recommended in *acute moderate-severe* traumatic brain injury patients (Type 2a recommendation, level A evidence). However, further studies are needed to both evaluate outcomes and to determine the optimal treatment protocols for the different types of injuries (Type 1 recommendation, level A evidence).

Hyperbaric oxygen threrapy should be recommended in *chronic traumatic brain injury* for a selected group of patients suffering from prolonged post-concussion syndrome who have clear evidence of metabolic dysfunctional brain regions as determined by neuroimaging (Type 2a recommendation, level B-R evidence). Patients should be properly evaluated by standardized cognitive tests and functional brain imaging (Type 1 recommendation, level B-R evidence).

Introduction

Epidemiology

Traumatic brain injury (TBI) is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, direct 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 [3]. Data are lacking on patients who have TBI evaluated in nonhospital settings or did not receive any medical care [4]. These data do not include the military or veterans administration systems [5]. TBI is noted to be the signature injury of the Afghanistan and Iraq military conflicts: 28% of the soldiers evacuated have TBI. 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 [6]. 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 [7]. 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 [8,9].

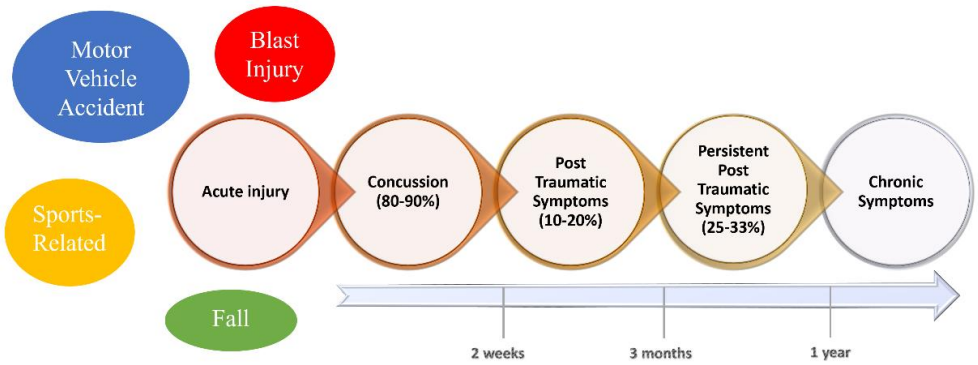
The health implications of TBI are multi-dimensional, dependent on the severity of TBI, and have a wide spectrum of physical, mental, social, and emotional disabilities. TBI also presents a considerable financial burden on individuals, families and national economies and health systems, with annual costs estimated at more than $56 billion [9].

Classification

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 duration of loss of consciousness (LOC), the presence of post-traumatic amnesia (PTA), and the Glasgow coma scale (GCS) grading of the level of consciousness.

According to one classification system, 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 [10]. 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) [11,12]. Most patients recover from PCS within weeks to months but up from 10 to 25% of the patients may experience prolonged PCS (PPCS) in which the symptoms become chronic and last for over six months [13-16] (Figure-1). Ten to 30% of the patients are classified as moderate to severe TBI if one or more of the following criteria apply: death, loss of consciousness for more than 30 minutes e, PTA of 24 hours or more, and GCS lower than in the first 24 hours to admission [10]. 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 [10]. 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 may suffer from significant physical disability in addition to cognitive, psychological and emotional impairments [17].

Figure-1: mTBI marching injury



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 [18]. Diffuse axonal injury is the hallmark lesion in moderate to severe TBI. The deceleration and acceleration forces most often associated with rotational forces cause axonal shear-strain, which results in cytoskeletal damage 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 [19-21].

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 raised intracranial pressure (ICP), metabolic changes, infection, hydrocephalus, release of excitotoxic levels of excitatory neurotransmitters, impaired calcium homeostasis and mitochondrial dysfunction [22,23].

The sudden stretching of the neuronal and axonal membranes initiates a flux of ions through previously regulated ion channels and transient physical membrane defects [24,25]. This process is followed by a widespread release of a multitude of neurotransmitters, particularly excitatory amino acids (EAAs) such as glutamate and aspartate [25,26], resulting in further changes of neuronal ionic homeostasis. Recent metabolomic profile found glutamate/glutamine, aspartate, GABA, other amino acid metabolism as well as to other amino acid metabolites involved in plasma membrane integrity are altered [27,28]. This post-traumatic ionic cellular derangement leads to mitochondrial calcium overloading [26,29], which is responsible for inducing changes of inner membrane permeability with consequent malfunctioning, uncoupling of oxidative phosphorylation, overproduction of reactive oxygen species (ROS), changes in mitochondrial proteins expression (such as pyruvate dehydrongenase) [30] and, finally, mitochondrial swelling and dysfunction. Mitochondrial complexes (mainly I and IV) activities drop, with reduction of ATP synthesis [31].

EAAs released in the process activate microglia, the first line of active immune defense in the central nervous system (CNS). When activated, microglia release a series of immune factors, including ROS, reactive nitrogen species, inflammatory cytokines and additional excitatory neurotransmitters [32]. This "immunoexcitotoxicity" response further disrupts mitochondrial function. The overall function is to remove the inciting pathogens and damaged brain tissue, yet if the excitatory environment persists, a chronic low grade inflammation may continue [33].

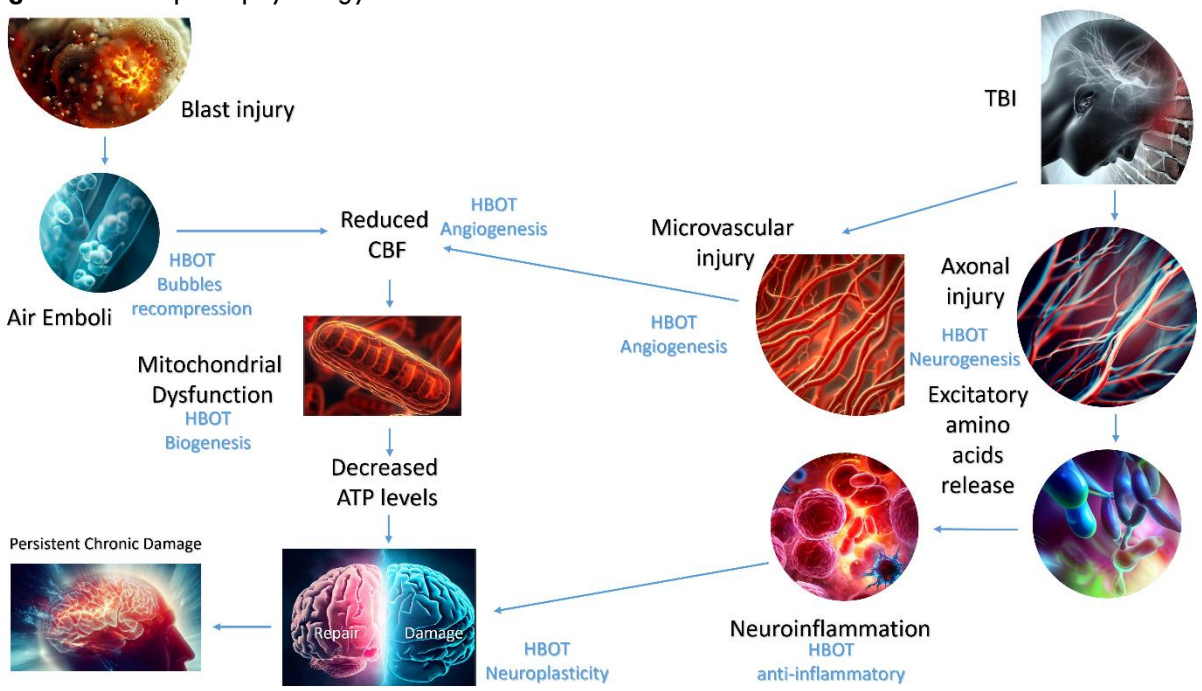
In addition to the axons, vascular elements in the grey-white matter junctions are sheared and damaged [34]. As the microvascular injury propagates, the regional cerebral blood flow/perfusion decreases and the injured brain suffers from hypoxia. In turn, mitochondria function, which is directly dependent on the partial pressure of oxygen, is further significantly decreased [35,36].

Thus, autoregulation, the maintenance of cerebral blood flow at appropriate levels during changes in systemic blood pressure, and global cerebral blood flow can be disturbed [37-40]. Impairment of the cerebral blood flow sensitizes the brain to secondary insults, such as hypotension, intracranial hypertension, and dehydration [38,41]. The reduced

cerebral blood flow further increases brain tissue hypoxia.

Due to mitochondrial dysfunction described above, during the time of maximum energy request, the neurons need to work overtime via the more rapid, but less efficient, oxygen-independent glycolysis which is unable to fulfill energy requirements [42]. These suggest that even mTBI may cause biochemical changes which lead to depressed brain energy generation and accordingly decreased brain metabolism [43,44]. Hypometabolism is likely to influence brain activation [44-46], reduce long-term potentiation and learning and decrease neural plasticity [47]. Since neurotrophins, such as brain-derived neurotrophic factor (BDNF) are regulated by neural activity, reduced metabolism decreases the synaptic facilitation and neurotransmitters release enhancement [48,49] (Figure-2)

Figure-2: PPCS pathophysiology and HBOT mechanisms of action



Current treatment

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 [22,23]. 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 [50-54]. Moreover different centers use different treatment plans and there is suboptimal compliance with current evidence-based practice guidelines for moderate-to-severe TBI patients [55-57].

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 physical therapy, speech and language therapy, cognitive rehabilitation therapy, medications and others [58]. However, several systematic reviews found limited evidence to support the efficacy of rehabilitation programs [59]. Many long term outcome studies concluded that patients with moderate-severe TBI show physical and functional improvement but remain with cognitive, emotional and neuro-psychosocial impairments. These patients demonstrate significant limitations in daily living tasks [60-63].

As stated above, up to 25% of PCS patients may develop chronic long term disabilities and PPCS [13-16]. 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 consequence of TBI [64]. 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 [64].

Hyperbaric oxygen therapy therapeutic mechanisms

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 [65]. 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 [66]. 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 [67].

HBOT can increase oxygen availability in the early period following TBI, reduce secondary injury and improve the long term outcome [68-72]. Improved brain tissue oxygenation has been shown to improve aerobic metabolism and decrease brain lactate concentrations in animal models [73,74] as well as in patients with severe TBI [75-77].

HBOT also improves cerebral vascular flow [75,78-80], promotes blood-brain barrier integrity, preserves mitochondrial membrane properties [71], reduces inflammatory reactions [81], reduces both microgliosis and astrogliosis reactions [82,83], decreases the lesion size [69,71] and brain edema, and reduces intracranial hypertension [69,84,85]. HBOT may induce resilient mitochondrial transfer from astrocytes to inflammation susceptible neuronal cells [86].

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 [70,80,87]. The elevated oxygen concentration in the blood and injured tissue during treatment [74,84,88] can supply the energy needed for the process of neuroplasticity.

HBOT induces neuroplasticity by stimulating cell proliferation [89], promotes neurogenesis of endogenous neural stem cells [90], regenerates axonal white matter [91], improves maturation and myelination of injured neural fibers [92,93], and stimulates axonal growth thus increasing the ability of neurons to function and intercommunicate. [94,95]. 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) [84,90,96]. Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells, including astrocytes [97]. The common denominator to all repair and regeneration mechanisms is that they are all oxygen dependent.

Hyperbaric oxygen therapy was also found to have a significant role in initiation and facilitation of angiogenesis, which is required for axonal regeneration [98-102]. Local or diffuse hypoperfusion, as in TBI, is a limiting factor for any regenerative process [103-107]. By inducing angiogenesis, HBOT improves the cerebral vascular blood flow necessary for neurogenesis and synaptogenesis [108,109]. See Figure-2 for summary of HBOT therapeutic mechanisms of action.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-P) 2015 guidelines [35]. No registration was needed for this study.

We performed a restricted search using the keywords “traumatic brain injury” [All Fields] OR “post-concussion syndrome” [All Fields] OR “TBI” [All Fields] OR “PCS” [All Fields] AND “oxygen” [MeSH Terms] OR “hyperbaric oxygen” [MeSH Terms] OR, “HBOT” [MeSH Terms] on 1st April 2023 within the following databases: Cochrane Library, PubMed, Google Scholar, and Web of Science. Time period included 1969 to April 2023. Basic inclusion filters were humans clinical data, English language.

We included studies of all type of patients who suffered a TBI of all severities (mild, moderate, severe), in both the acute, subacute and chronic stages who underwent HBOT intervention of any duration and protocol, We included the following exclusive types of studies: (1) those evluating the efficacy of the use of HBOT in patients’ cognitive function, neurological status, self-reported symptoms, imaging and electroencephalogram of TBI patients. (2) those assesing the safety of HBOT used to treat TBI patients.

All types of HBOT protocols, pressure, duration, air breaks, chambers were considered. Studies were included whether the investigators compared HBOT to placebo, a standard of care or no control.

We included randomized controlled studies, prospective studies, retrospective studies, case series and case reports. We inlcluded both

controlled and uncontrolled studies. We excluded reviews and letters.

The primary outcome was a patients outcomes in either cognitive, motor, self reported symptoms or functional status. Secondary outcomes included adverse events.

Two authors (A.H. and S.E) independently screened titles and abstracts of all identified articles, and full-text copies of all relevant articles were acquired. Disagreements were resolved by consensus and discussion with a third reviewer was not required.

The two authors (A.H and S.E) independently evaluated quality of each included study (see Table-3 for level of evidence). In case of disagreement concerning the risk of bias, discussion was performed including a third reviewer (J.M) to resolve the issue.

Articles were first categorized into two main categories, acute-subacute TBI and chronic TBI according to timing of intervention. Clinical outcomes and adverse events were evaluated separately. Next, each article was further classified into low (case report, case series), medium (prospective clinical study) or high-level quality (randomized controlled study).

Results

The database search (up to April 1st 2023) retrieved 1765 unique citations of which 1653 were excluded based on title and abstracts (Figure-3). We assessed 109 full-text articles for eligibility and 51 studies were included.

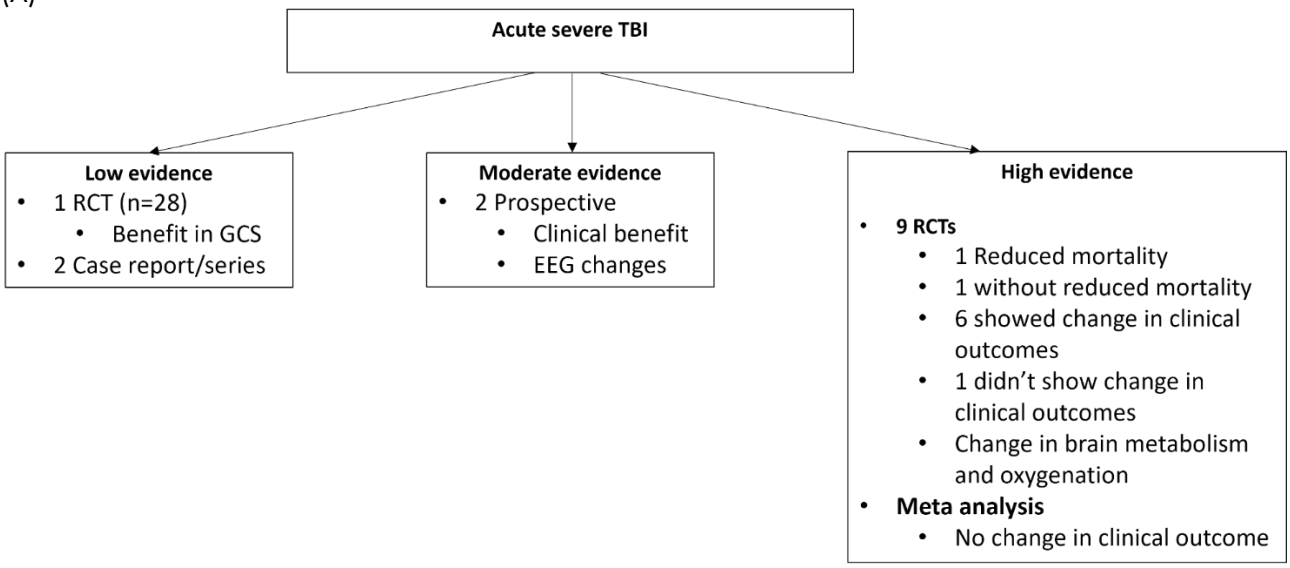
Hyperbaric oxygen therapy in acute severe traumatic brain injury

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 (1.5-2.5 absolute atmospheres (ATA), 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. Evidence is summarized in Figure-3A and Table-4.

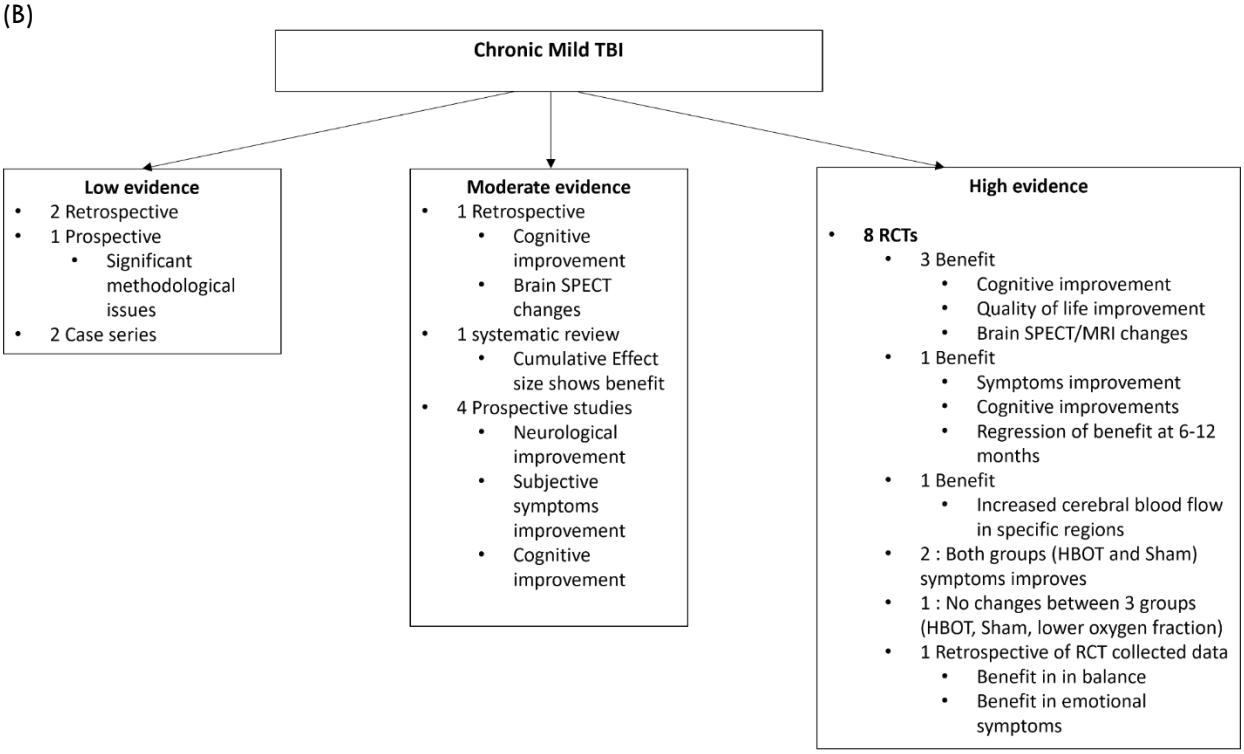
Figure-3: Evidence summary

(A) Acute severe TBI evidence, (B) Chronic mild TBI evidence, (C) Chronic severe TBI evidence

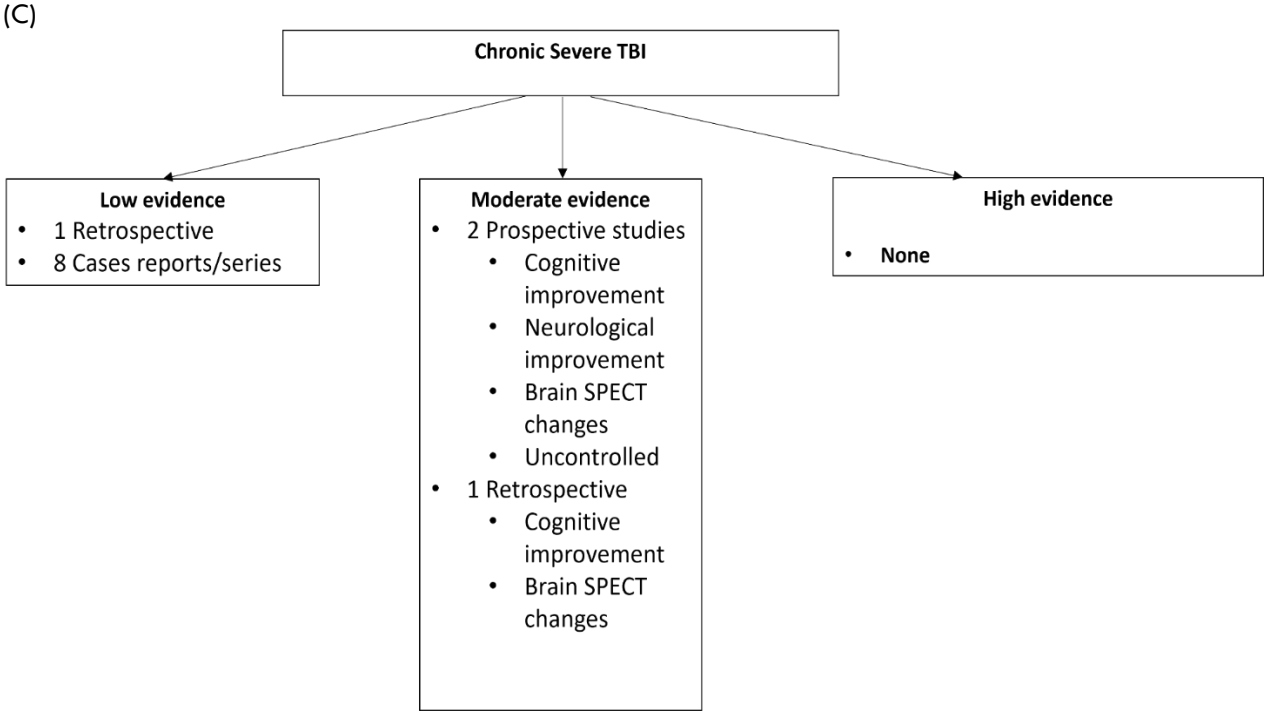
(A)



(B)



(C)



The studies used mostly 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.

Hyperbaric oxygen therapy in acute severe traumatic brain injury – low level evidence

Parkash's RCT [110] 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 [111] reported benefit on specific types of brain injuries: acute subdural hematomas and mild to moderate diffuse axonal injuries were improved while severe diffuse axonal injury did not. However, in addition to the retrospective nature of this data, the statistical analysis is lacking and the HBOT protocol is unclear. Lee et al. [112] described a significant complication of HBOT in the acute trauma setting. The patient who had a skull base fracture, suffered from a tension pneumocephalus during the HBOT session, which mandated an emergent surgery. Hence unrepaired skull base fractures and CSF leaks were suggested as contraindications.

Hyperbaric oxygen therapy in acute severe traumatic brain injury – moderate level evidence

A prospective study done by Mogami [113] 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. Neither statistical analysis nor severity of injury were given.

Zhong et al. [114] performed a prospective study on 88 severe TBI patients. Patients were randomized to either standard of care or HBOT with the first session started one week from admission, while the other half continued standard of 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 National Institutes of Health Stroke Scale (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 (4.1±1.1) and number of sessions (5.6±1.9) as well as lack of a true sham control group.

Hyperbaric oxygen therapy in acute severe traumatic brain injury – high level evidence

The largest randomized controlled trial (RCT) in severe TBI patients, conducted by Rockswold [115], 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 ICP 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 [116], Rockswold focused on brain metabolism and oxygenation rather than the clinical effects in 69 patients (26 treated by HBOT) with severe acute TBI [116]. 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 ICP ($p<0.001$) 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 [117] 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 [118] 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 were also a significant reduction in abnormal brain activity ($p<0.01$), improved brain perfusion and decreased cerebral vascular resistance ($p<0.01$) [119]. 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. [120] 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 [121] 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 [122] 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.

The randomized controlled trial in the late 70's by Artu [123] 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 (10 sessions were followed by 4 days of rest and repeated in cases which did not respond).

Meta-analysis done at 2012 [124] 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.

Lu et al. [125] conduced a multicenter randomized controlled trial on 158 patients with moderate-severe TBI 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.

Hyperbaric oxygen therapy in acute severe traumatic brain injury – adverse events

No significant side effects were reported in all above mentioned 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 [124].

Hyperbaric oxygen therapy in chronic severe traumatic brain injury

There were 2 prospective studies, 2 cohort studies and 8 case reports evaluating the clinical effects of HBOT in patients suffering from severe TBI in the chronic stage. No randomized controlled trial was performed and both prospective and retrospective studies were uncontrolled. Apart of one study, most studies had a small sample size (1-20 patients). In addition, there were a great variabilities in inclusion criteria, timing of injury, number of sessions, HBOT protocol and clinical outcome measures between the studies. Evidence are summarized in Figure-3B and Table-4.

Hyperbaric oxygen therapy in chronic severe traumatic brain injury – low level evidence

Sanhi et al. performed retrospective analysis [126] 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 included its retrospective nature, unclear inclusion criteria, grouping of patients in the and unreported p-values.

Wright et al. reported on a case series [127] 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 of the few reports of military men whose symptoms of chronic PPCS improved after HBOT. Ly LQ et al. series [128] 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. Hardy reported [129] 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 [130] 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 [131]. 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 reported by Lee et al. suggested that tension pneumocephalus is a rare complication that may occur in unrepaired skull base fractures [132]. A case by Skiba et al. [133] 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. [134] 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.

Hyperbaric oxygen therapy in chronic severe traumatic brain injury – moderate level evidence

Churchill published a prospective study [135] 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.

Barrett KF performed a non-randomized prospective study [136] 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 [137] on a military service veteran with chronic PCS and PTSD who experienced improved clinical symptoms and brain perfusion in bilateral frontal and temporal areas.

Hadanny et al. [138] analyzed the largest cohort of 154 chronic TBI patients treated with HBOT, out of which 61 (39%) were severe TBI cases. HBOT was associated with significant improvement in all of the cognitive domains, where 23-44% of patients had large improvements. Cognitive function changes correlated with increased activity in relevant brain regions evaluated with SPECT.

Hyperbaric oxygen therapy in chronic mild traumatic brain injury

There were 7 randomized controlled trials (RCT), 6 prospective studies and 4 cohort studies evaluating the clinical effects of HBOT in patients suffering from mTBI 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. Evidence are summarized in Figure-3A and Table-4.

Hyperbaric oxygen therapy in chronic mild traumatic brain injury – 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 [139]. 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 included a relatively small sample and lack of control group.

Shi et al. [140] 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 [141] 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 with potential secondary gain.

Shandley et al. [142] 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. [143] 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.

Hyperbaric oxygen therapy in chronic mild traumatic brain injury – moderate level evidence

Golden Z et al. prospective study [144] 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.

Shi et al. RCT [145] 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.

Hadanny et al. [138] 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.

Hart et al. performed a systemic review [146] of all four the DoD studies (see above) including 254 TBI patients. The pooled analyses indicated trends toward improvement in the subjective questionnaires (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.

Harch et al. [147] 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 HBO protocol including two daily sessions.

Mozayeni et al. [148] 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. [149] 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.

Ablin et al. [150] recently conducted a prospective active-control study on 64 mTBI patients who suffer from fibromyalgia. Patients were randomized to either 60 sessions of HBOT (2ATA, 100% oxygen) or the standard recommended pharmacological treatment (Pregabalin or Duloextine) for 3 months. HBOT demonstrated a significant decrease in pain intensity (d=0.95, p=0.001), fibromyalgia syndrome severity measures (d=1.04, p<0.001) and increase in quality of life (d=1.08, p<0.001), compared to medications. Additionally, both pain thresholds (d = 1.11, p = 0.0001) and conditioned pain modulation measures were signifcantly increased by HBOT (d = 0.72, p = 0. 016). The clinical changes correlated with significant changes in brain metabolism in the left frontal and right temporal cortex, as evaluated by brain SPECT (r=0.455, p<0.001). The imaging-clinical correlation provides an objective confirmation of a therapeutic effect which was not seen in the medications group. The lack of long term evaluations and the use of medications as an active control rather than a sham controlled intervention.

Hyperbaric oxygen therapy in chronic mild traumatic brain injury – high level evidence

Wolf's double-blind RCT on 50 military servicemen [151] suffering from mild TBI symptoms compared HBOT of 2.4 ATA to the previously considered as "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 statistically significant differences between the groups (p=0.35 for 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. First, the use of 1.3 ATA as sham treatment is a known today to be low dose rather than placebo.

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 other related symptoms could have been included without any direct injury at the brain tissue level.

Cifu's RCT [152,153], 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 found significant differences between the groups, except for several items in group 2 and group 3, with regards cognitive functions, RPQ questionnaire or eye-movements (p>0.05 for all measures). Cifu's study has several drawbacks, similar to those of the study by Wolf et al. 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 or other veterans suffering from PPCS (drugs that were not proved to have any beneficial effect in PCS or 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, other co-morbidities such as for example mental or mood disorders were not excluded so it is not a clear PCS study.

Miller et al. RCT [154], 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", which is actually low dose, and HBOT groups. However, there were no significant differences between the HBOT and "sham", 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). 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 military men (a) with obvious secondary gains; (b) The RPQ questionnaire with its methodological problematic issues was used as the primary outcome indicator and (c) no objective brain imaging were done as endpoints or as an inclusion criteria.

Boussi-Gross et al. RCT [155] 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. 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. [156], 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 [157] reported the eye tracker 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. Several limitations should be mentioned. First, included subjects were composed of a mixed group of both active military men and veterans, with potential secondary gains. Second, patients' selection was not made based on objective imaging, even when performed. Third, there were significant breaks in patients' protocol with 40 daily sessions given in 12 weeks rather than 8. Fourth, intention to treat included over 7 patients (20%) who did not receive the designated protocol. Fifth, PTSD comorbid was a significant cofactor which was not excluded. Lastly, as mentioned above, the control protocol of 1.2 ATA could not be considered as a true sham.

Hart et al. [158] 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. [159] 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. [160] 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. [161] 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 (1.3ATA), 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. [162] 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 [155]. 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 sustained 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.

Hadanny et al. [163] randomized 25 children (age 8-15) suffering from PPCS, 6 months-10 years after a mild-moderate TBI in a new sham-controlled protocol. Both groups (HBOT, N=15, Sham, N=10) underwent 60 sessions of either HBOT (1.5 ATA, 100% oxygen) or Sham (1ATA, 21% oxygen). The authors provided proof of successful patients' blinding. The study endpoints included objective cognitive tests, parents based quality of life, PPCS symptoms and behavioral questionnaires and brain imaging. The HBOT group showed significant improvements in the general cognitive score ($p = 0.01$), memory ($p = 0.02$), executive function ($p=0.003$), PPCS symptoms including emotional score ($p = 0.04$), behavioral symptoms including hyperactivity ($p = 0.03$), global executive composite score ($p = 0.001$), planning/organizing score ($p = 0.007$). Additionally, there were significant mean diffusivity (MD) decreases in the HBOT group compared to the sham group in specific brain regions, which correlated with cognitive changes. Nine out of the 10 (90%) sham patients and 13/15 (86.7%) patients from the HBOT group had mild side effects ($p = 1$), which were treated conservatively.

Aside of being the first study to evaluate the use of HBOT in pediatric PPCS, the study demonstrates a unique inert true sham with effective blinding along with objective evaluations. The correlation between cognitive function and diffusion imaging changes provides an additional validation of the findings. The study's main limitations include considerably low sample size and the lack of long-term evaluations.

Hyperbaric oxygen therapy in chronic mild traumatic brain injury – adverse events

Most studies did not report any significant side effects. In Harch study [141], 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. [164] 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. [165] 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%).

Discussion

Acute traumatic brain injury

Summarizing the acute setting meta-analyzing we can conclude that the data is difficult to interpret due to the variety of treatment protocols and evaluation time points. However, HBOT in the acute-subacute setting after TBI improves both functional status (GOS, GCS) and metabolic outcomes (monitored with invasive brain microdialysis probe) [115 116 117 118 124]. Mortality, as a hard end-point, was significantly reduced in all studies that used it as an end point [115 117 124]. 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 [116 117 118 124 120 121 125].

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 [166].

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

Recommendations in Acute traumatic brain injury – patient Selection

Most studies in the acute-subacute settings evaluated moderate-severe TBI [116 117 118 124 120 121 125]. 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 hyperbaric chamber. Currently, there is not enough evidence for the specific sub-types of injuries that can benefit the most 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.

Recommendations in Acute traumatic brain injury – hyperbaric oxygen therapy protocol

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 [117]. The use of pressures higher than 2 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 once daily sessions.

Myringotomy should be performed in all patients in order to avoid ICP elevation during the treatment [115].

Cost impact of hyperbaric oxygen therapy in acute traumatic brain injury

Financially: A previous cost-benefit analysis in TBI [167] 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 traumatic brain injury

Meta-analyzing the data is complex due to the variety of treatment protocols and different methods of evaluation and patients selection. There have been several RCTs but most of them had considerable methodological flaws [151 152,153 154 156].

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 [155,162].

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).

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

Recommendations in chronic traumatic brain injury – patient selection

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 [151 152,153 154 156 155 162]. 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 [155 138]. Therefore, patients should have brain SPECT or other functional brain imaging performed, and be selected for HBOT if they demonstrate considerable metabolism defects.

Recommendations in chronic traumatic brain injury – hyperbaric oxygen therapy protocol

Most evidence for HBOT in the chronic PPCS setting was gained with a protocol of 40-60 daily sessions of 60 minutes at 1.5 ATA. Doses higher than 2 ATA were not proven beneficial, but the evidence is inconclusive as the relevant studies were poorly designed. Even though lower pressure, such as 1.3 ATA, can also be effective, at this point in time we have more reliable data available on 1.5 ATA, and the safety profile of 1.5 ATA is considered very high.

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. 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 of hyperbaric oxygen therapy in chronic traumatic brain injury

Financially: The cost per year of a patient with PPCS is about $32,000 [168]. 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.

Limitations

Limitations of this study include the presence of significant heterogeneity, variations in the different populations, different HBOT protocols (dose, time, type of therapy) and different outcomes reported, In addition, very little studies reported length of stay and long term functional outcomes.

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
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

Conclusions

Acute-subacute traumatic brain injury: Based on the data available today, HBOT may be recommended in acute moderate-severe TBI patients (Type 2a recommendation, level A evidence, Tables 2-3) to reduce mortality. However, there are contradictory results on functional outcome (Type 2b recommendation, level A evidence, Tables 2-3) and further studies are needed in order to both confirm outcomes and the optimal treatment protocol for the different types of injuries (Type 1 recommendation, level A evidence, Tables 2-3). Myringotomy should be considered in all cases when there is no possibility for self-equilibration of pressure. (Type 3 recommendation, level C evidence, Tables 2-3).

Chronic traumatic brain injury: Based on the data available today, HBOT should be recommended in chronic TBI for a selected group of patients suffering from PPCS who have clear evidence of metabolically dysfunctional brain regions (Type 2a recommendation, level B-R evidence, Tables 2-3). 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, Tables 2-3).

Conflicts of interests

AH work for AVIV Scientific LTD. SE the head of the medical advisory board and a shareholder at AVIV Scientific LTD. JM is a member of the medical advisory board at AVIV Scientific LTD .

Table-4: Evidence summary

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Ablin 2023 [150]	Prospective	64 chronic mTBI induced fibromyalgia (29 HBOT, 29 medications)	(1) Pain intensity VAS score (2) Psychological questionnaires (3) Pressure pain threhsold, (4) Brain activity using SPECT	90 min of 100% oxygen at 2 ATA X 60 sessions	HBOT vs Medications: Improvements in (1), (2), (3), (4)	Favors the use of HBOT in TBI induced fibromyalgia Active control using the standard recommended treatment Limitations:no long term evaluations, active control instead of sham intervention
Hadanny 2022 [163]	RCT	25 chronic pediatrics PPCS patients (15 HBOT, 10 SHAM)	(1) Cognitive function (2) Psychological questionnaires (3) Balance (4) Imaging: Brain MRI diffusion tensor imaging (DTI)	60 min of 100% at 1.5 ATA oxygen X 60 sessions	HBOT Vs SHAM: Improvements in (1) (2), (3), (4)	Favors the use of HBOT in pediatric PPCS Randomized controlled trial with true inert sham protocol Limitations: small sample size, no long term evaluations
Lu 2021 [125]	RCT	158 acute moderate-severe patients (42 Rehab, 39 Rehab + HBOT, 39 Intense Rehab +HBOT, 38 Intense Rehab	(1) Functional (2) Cognitive	60 min of 100% at 2 ATA X 60 sessions in 3 courses of 20 with 10 day interval in-between	All groups improvemens in (1) and (2) Remarkable improrvments in HBOT+Intense rehab	Favors the use of HBOT Limitations: No sham control, 10 days break between HBOT courses
White 2021 [134]	Case report	1 acute severe TBI from MVA, HBOT combined with neurofeedback	(1) Clinical evaluation (2) cognitive evaluation	165 sessions	Improvements in (1) and (2)	Case report Limitations: Uncontrolled, large number of HBOT session
Biggs 2021 [149]	Retrospective / Systematic review	12 previous studies on chronic TBI	Effect sizes of (1) symptomatic effects, (2) cognitive effects	Variable	Large effect size in (1) and (2)	Favors the use of HBOT Limitation: statistical analysis of previous studies
Ma 2021 [161]	Prospective study	28 patients: 14 firefighters suffering from chronic mTBI, 14 healthy controls	(1) Cerebral blood flow in Perfusion MRI	45 min of 100% at 1.3 ATA X20 sessions	HBOT vs healthy: Improvement in (1)	Favors the use of HBOT Limitations: No clinical evaluations, no sham control, small sample size
Skiba 2021 [133]	Case report	1 acute severe TBI from MVA	(1) Clinical evaluation (2) Psychological evaluation (3) Cognitive evaluation	90 min of 100% at 2 ATA X 42 sessions, variable (3-5) sessions per week	Improvement in (1), (2), (3)	Case report Limitations: Uncontrolled, variable sessions per week
Harch 2020 [162]	RCT	52 military and civilian chronic mTBI patients (HBOT n=25, Control n=27)	(1) Symptoms questionnaires (2) Cognitive (3) Psychological questionnaires	60 min of 100% at 1.5 ATA X 40 sessions	HBOT vs control: Improvements in (1), (2), (3)	Favors the use of HBOT Limitations: Sample size, Lack of objective based patients' selection, no sham control group

Zhong 2020 [114]	Prospective	88 severe TBI patients (44 HBOT, 44 control)	(1) Clinical (GCS) (2) Clinical (NIHSS)	120 min of 100% at 2-2.5ATA X 30 sessions	HBOT vs control: improvements in (1) and (2)	Favors the use of HBOT Limitations: Variable timing from injury, variable number of sessions, no Sham control group
Hart 2019 [146]	Meta Analysis	254 chronic mTBI patients	(1) Psychological questionnaires (2) Cognitive	40 sessions– variable protocols	HBOT vs Sham: Improvements in (1) and (2), Dose response	Favors the use of HBOT Limitations: Military men, active sham treatment, variable protocols, no patients selection
Mozayeni 2019 [148]	Prospective study	32 chronic mTBI patients	(1) Clinical (2) Psychological questionnaires (3) Cognitive:	60 min of 100% at 1.5 ATA X 40-82 sessions	Improvement in (1), (2) , (3)	Favors the use of HBOT Limitations: Uncontrolled, mixed population, mixed variable treatment protocol
Shytle 2019 [143]	Case series	3 chronic mTBI patients	(1) Mood scales (2) Cognitive scales	60 min of 100% at 1.5-1.75 ATA X 20-30 sessions	Improvement in (1), (2)	Case series Limitations: Uncontrolled, variable protocols
Meehan 2019 [159] Walker 2019 [160]	Retrospective analysis of RCTs	71 chronic mTBI patients HBOT, 75 healthy controls	(1) Balance and Gait Measures (2) Sleep measures	60 min of 100% at 1.5 ATA X 40 sessions	HBOT vs Healthy: Improvements in (1) and (2)	Favors the use of HBOT Limitations: Mixed and imbalanced populations, protocol assurance, mixed interventions (HBOT/sham), Comorbidities
Weaver 2018 [156] Wetzel 2019 [157] Hart 2019 [158]	RCT	71 chronic mTBI patients HBOT n=36, Sham n=35	(1) Symptoms questionnaires (2) Psychological questionnaires (3) Cognitive (4) EEG (5) Eye tracking (6) Neuroimaging (7) Auditory (8) Vestibular (9) Labratory	60 min of 100% at 1.5 ATA X 40 sessions	HBOT vs Sham: Improvements in (1), (2), (3), (5), (8) Regression of results at 6 and 12 months	Favors the use of HBOT with short term effect Limitations: Mixed group of both active military men and veterans, no objective patients' selection 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
Hadanny 2018 [138]	Retrospective	154 chronic TBI patients (all severities)	(1) Cognitive	60-90 min of 100% at 1.5-2 ATA X40–70 sessions	Improvement in (1)	Favors the use of HBOT Limitations: Retrospective, no control group, no long term evaluation. variable protocols, variable number of sessions

Harch 2017 [147]	Prospective study	30 chronic mild-moderate TBI patients , 29 healthy controls	(1) Cogntive (2) Symptoms questionnaires (3) Psychological questionnaires (4) brain SPECT imaging	60 min of 100% at 1.5 ATA, twice daily X 40 sessions	Improvement in (1), (2), (3). HBOT vs Healthy: Improvement in (4)	favors the use of HBOT Limitaions: mixed population of active military men and veterans, no exclusion of comorbidities
Shandley 2017 [142]	Prospective	28 chronic mild-moderate TBI patients	(1) Cognitive (2) Symptoms questionnaires (3) Stem cells count	?	Improvement in (1), (2), (3)	Favors the use of HBOT Limitations: Uncontrolled
Tal 2015 [139]	Case series	10 chronic patients	(1) Cognitive (2) Brain MRI perfusion imaging	60 min of 100% at 1.5 ATA X 60 sessions	Improvement in (1) and (2)	Favors the use of HBOT in mTBI Limitations: Small sample. no control group
Wolf 2012 [151]	Randomized controlled trial	50 chronic mTBI patients (25 HBOT, 25 Sham)	(1) Symptoms questionnaires (2) Cognitive	90 min of 100% at 2.4 ATA X 30 sessions	Both groups improved in (1) and (2) more than expected No difference between HBOT and Sham	No conclusion Both groups improved more than would be expected greater than 6 months after mTBI. Limitations: Selection of military service men as patients, secondary gain effect, 1.3 ATA as placebo, no exclusion of depression, PTSD or other comorbidities
Cifu 2014 [152] Cifu 2013[153]	Randomized controlled trial	61 chronic mTBI patients (19 and 21 HBOT 21 Sham)	(1) Clinical (2) Symptoms questionnaires (3) Psychological questionnaires (4) Eye movements	Group 1: 60 min of 75% at 2 ATA X 40 sessions Group 2: 60 min of 100% at 2 ATA X 40 sessions	HBOT vs Sham: No significant interaction for any measure	No conclusion Limitations: 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
Miller 2015 [154]	Randomized control trial	72 chronic mTBI patients (23 TBI care, 24 HBO + TBI care, 25 Sham +TBI care)	(1) Symptoms questionnaires (2) Cognitive (3) Psychological questionnaires	60 min of 100% at 1.5 ATA X 40 sessions	Both HBOT and Sham improved in (1) (2) and (3) more than expected, no change in TBI care only No difference between HBOT and Sham	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
Boussi-Gross 2013 [155]	Randomized controlled trial, crossover design	56 chronic PPCS patients (32 HBOT, Control/ Crossover	(1) Cognitive (2) Quality of life (3) Brain SPECT imaging	60 min of 100% at 1.5 ATA X 40 sessions	HBOT vs Control: Improvement in (1), (2), (3)	Favors the use of HBOT Strengths: Randomized controlled trial with control group and crossover design, selection of patients with proper functional imaging

*Churchill 2012 [135]	Prospective study	28 chronic TBI patients	(1) Cognitive (2) Psychological questionnaires (3) Clinical	60 min of 100% oxygen at 1.5 ATA X 60 sessions	Improvement in (1), (2), (3)	No conclusion due to: Small sample size, Vague inclusion criteria, no control group
Rockswold 2013	Randomized controlled trial	42 acute severe TBI patients (22 HBOT, 20 control)	(1) Mortality (2) Functional outcome (3) Intracranial measures	60 min of 100% oxygen at 1.5 ATA followed by 3 hours 100% at 1 ATA X 3 sessions	HBOT vs control: Improvements in (1), (2), (3)	Favors HBOT use in acute severe TBI Limitations: sample size
Bennett 2012 [124]	Meta-analysis	571 acute severe TBI patients (285 HBOT, 286 control)	(1) Mortality (2) Functional outcome	40-60 min of oxygen 100% at 1.5-2.5 ATA X 3-10 sessions	HBOT vs Control: Improvement in (1) and (2)	Favors HBOT use in acute severe TBI Limitations: variable protocols
Prakash 2012 [110]	Randomized controlled trial	56 acute severe TBI children (28 HBOT, 28 control)	(1) Functional outcome (2) hospitalization duration	3 sessions at 1 week interval, others parameters unknown	HBOT vs control: Improvements in (1) and (2)	Favors the use of HBOT in acute severe TBI Limitations: sample size, statistics unpublished
Sahni 2012 [126]	Retrospective analysis	40 acute severe TBI patients (20 HBOT, 20 control)	(1) Functional outcome	60 min of 100% at 1.5 ATA X 30 sessions	HBOT vs Control: Improvement in (1)	Favors the use of HBOT in severe TBI Limitations: sample size, statistics unpublished
Harch 2012 [141]	Case series	16 chronic mild-moderate TBI patients	(1) Symptoms questionnaires (2) Psychological questionnaires (3) Cognitive (4) Brain SPECT imaging	60 min of 100% at 1.5 ATA X 40 sessions	Improvement in (1), (2), (3)	No conclusion Limitations: No control group, sample size, secondary gain of military subjects
Lee 2012 [132]	Case report	1 acute severe TBI patient	None	Unknown	Tension pneumocephalus	Case report Rare side effect report
Lv LQ 2011 [128]	Case series	6 acute severe TBI patients	(1) Paroxysmal sympathetic hyperactivity	Unknown	Improvement in (1)	No conclusion Limitations: case series, sample size, no control group
Rockswold 2010 [116]	Randomized controlled trial	69 acute severe TBI patients: 26 HBO + standard care, 21 normobaric hyperoxia + standard care, 22 standard care	(1) Intracranial measures	90 min of 100% at 1.5 ATA X 3 sessions	HBOT vs Control: Improvement in (1)	Favors the physiological effect of HBO in acute severe TBI
Mao 2010 [120]	Randomized controlled trial	60 acute severe TBI patients (30 HBOT +standard treatment, 30 standard treatment)	(1) Functional outcome (2) EEG changes	Unknown protocol	HBOT vs Control: Improvement in (1) and (2)	Favors the use in acute severe TBI Limitation: use of GCS score as a continuous parameter
Wright 2009 [127]	Case report	2 chronic TBI patients	(1) Symptoms (2) Cognitive	60 min of 100% at 1.5 ATA X ?	Improvement in (1) and (2)	Case report
Harch 2009 [137]	Case report	1 chronic mTBI patient	(1) Symptoms (2) Brain SPECT imaging	60 min of 100% at 1.5 ATA	Improvement in (1) and (2)	Case report

				for X 39 sessions		
Lee 2009 [112]	Case report	1 acute severe TBI patient	None	unknown	Tension pneumocephalus	Case report Rare side effect report
Lin JW 2008 [121]	Randomized controlled trial	44 acute severe TBI patients (22 HBOT, 22 control)	(1) Functional outcome	90 min of 100% at 2 ATA X 20 sessions	HBOT vs Control: Improvement in (1)	Favors HBO for subacute TBI Limitations: No analysis per severity, GCS as continuous parameter
Xie 2007 [122]	Randomized controlled trial	60 acute severe TBI patients (30 HBOT + neurosurgical care, 30 neurosurgical care)	(1) Functional outcome (2) Blood inflammation marker	80 min of 100% at 2-2.5 ATA X2-10 sessions	HBOT vs Control: Improvements in (1) and (2)	Favors the use of HBO in acute TBI Limitations: GCS as continuous parameters, variable number of sessions, no analysis per severity
Hardy 2007 [129]	Case report	1 chronic severe TBI patient	(1) EEG changes (2) Cognitive (3) Clinical (4) SPECT brain imaging	60 min of 100% at 2 ATAX20 sessions + 60 sessions 1 year later	Improvement in (1), (2) and (3)	Case report
Shi XY 2006 [140]	Prospective study	310 subacute-chronic patients	(1) Brain SPECT imaging (2) Brain CT imaging	90 minutes of 96% at 2 ATA X 20 sessions	Improvement in (1)	No conclusion Limitations: No control group, unknown clinical value
Golden Z 2006 [144]	Prospective study	63 chronic TBI patients (42 HBOT, 21 control)	(1) Cognitive	unknown	HBOT vs Control: Improvement in (1)	Favors the use of HBOT in brain injury Limitations: Unknown chronic brain injury source, unknown HBOT protocol, nonrandomized controlled
Barrett KF 2004 [136]	Prospective	5 chronic TBI HBOT, 5 chronic TBI controls, 5 normal controls 68 normal controls for SPECT controls	(1) Cognitive (2) Psychological questionnaires (3) Symptoms (4) Brain SPECT imaging	60 min of 100% at 1.5 ATA X 80 sessions + 40 sessions after 5 months	HBOT vs Control: No changes	No conclusion Limitations: Small sample size, no randomization
Mitani 2004 [111]	Case series	Unknown	(1) Functional outcome	Unknown	Unknown	No conclusion
Shi XY 2003 [145]	Randomized controlled trial	320 chronic TBI patients (195 HBO + medication, 125 medication only)	(1) Symptoms (2) Brain SPECT imaging	90 min of 96% at 2 ATA X 20-40 sessions	HBOT vs Medications: Improvements in (1) and (2)	Favors the use of HBO in TBI Limitations: Unknown inclusion criteria, Variable number of sessions
Ren H 2001 [118]	Randomized controlled trial	55 acute severe patients (35 HBOT +	(1) Functional outcome (2) Brain imaging: electric activity mapping (BEAM)	40-60 min of 100% at 2.5 ATA	HBOT vs Control:	Favors HBO for acute TBI

		standard care, 20 standard care)		X 30-40 sessions	Improvements in (1) and (2)	Limitations: GCS as continuous parameter, variable number of sessions
Woolley SM 1999 [130]	Case report	1 chronic severe TBI patient	(1) Postural stability (2) Gait	60 min of 100% n at 1.5 ATA, bi-daily X 40 sessions	Improvement in (1) and (2)	Case report
Neubauer RA 1994 [131]	Case report	1 chronic severe TBI patient	(1) Clinical (2) Cognitive (3) Brain SPECT imaging	Unknown time of 100% at 1.5-1.75 ATA X 188 sessions	Improvement in (1), (2), (3)	Case report
Rockswold 1992 [115]	Randomized controlled trial	168 acute severer TBI patients (84 HBOT +standard care, 82 standard care)	(1) Mortality (2) Functional outcome (3) Intracranial measures	60 min of 100% at 1.5 ATA, three-time daily X 21 sessions	HBOT vs Control: Improvement in (1)	Favors the use of HBO in acute TBI
Artru 1976 [123]	Randomized controlled trial	60 acute severe TBI patients (31 HBOT, 29 standard care)	(1) Mortality (2) Functional outcome	60 min of 100% at 2.5 ATA X 10 daily sessions followed by 4 days rest and repeat if not responding	No changes in (1) and (2) Subgroup analysis showed young patients with brainstem injuries improved in (2)	No conclusion Limitations: HBOT protocol was intermittent and inconsistent
Mogami 1969 [113]	Prospective study	66 acute severe TBI patients (51 TBI)	(1) Symptoms (2) EEG (3) Intracranial measures	30-60 min of 100% at 2-3 ATA X ? sessions	Improvements in (1), (2) and (3)	Favors the use of HBO in acute TBI no control group, variable number of sessions, no statistical analysis

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