Effect of hyperbaric oxygenation therapy on post-concussion syndrome (Review)

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Abstract. The present review evaluated the effect of hyperbaric oxygenation (HBO) therapy on post-concussion syndrome (PCS). Searches for publications from the earliest date possible up until the first week of 2016 were conducted using the electronic databases Cochrane, EBSCOhost, Embase, Ovid MEDLINE, PubMed and Web of Science. Additional trials were identified through reference list scanning. Randomized controlled trials assessing the effectiveness of HBO therapy in PCS were selected and tested for eligibility for inclusion in the present review. Two independent reviewers conducted data extraction and the Cochrane Collaboration's recommended method was used to assess the risk of bias in each study included. Review Manager 5.3 software was used for data synthesis and analysis and the standardized mean difference (SMD) or mean difference (MD) was estimated with a fixed or random effects model using a 95% confidence interval (CI). A total of 127 articles were identified, 4 of which were eligible for final analysis. The meta-analysis identified no difference in the Rivermead Post-Concussion Symptoms Questionnaire (MD=1.23; 95% CI, -3.47-5.94; P>0.05; I^2=35%) or Post-Traumatic Stress Disorder Checklist (PCL) scores (SMD=0.12; 95% CI, -0.31-0.54; P>0.05; I^2=0%) scores between groups receiving different oxygen doses. The differences in PCL scores (SMD=-0.13, 95% CI, -0.80-0.53; P>0.05; I^2=63%) and neurobehavioral symptoms (SMD=-1.00, 95% CI, -2.58-0.58; P>0.05; I^2=92%) between the HBO and sham groups were not significant. The current study demonstrated that HBO therapy has no significant effect on PCS compared with the sham group. Therefore, it was determined that effective design and execution of a large clinical trial, which includes treatment, control and sham groups is required in the future.

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Abbreviations: HBO, hyperbaric oxygenation; ATA, atmospheres absolute; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; NSI, Neurobehavioral Symptom Inventory; PCL, Post-Traumatic Stress Disorder Checklist; EQ-5D, EuroQoL Group's 5-dimension questionnaire

Key words: post-concussion syndrome, hyperbaric oxygenation, review

Contents

1. Introduction

Traumatic brain injury (TBI) is a major cause of death and disability that disproportionately affects young adults (1). The persistence of symptoms for >3 months following the onset of mild TBI is known as post-concussion syndrome (PCS). The incidence of PCS following the onset of TBI is ~15% after 3 months and 3-5% after 1 year (2). Common post-concussion symptoms include headaches, balance problems, sleep disturbance, fatigue, forgetfulness, poor concentration, irritability and anxiety (3). There are currently few established therapies available to treat patients with persistent PCS.

Hyperbaric oxygenation (HBO) therapy is currently used to treat acute and chronic ischemic injuries. HBO has well established theoretical underpinnings and is able to treat dive-related injuries, soft tissue injuries and carbon monoxide poisoning (4). The results of several studies have provided inconclusive evidence for the efficacy of HBO therapy in treating patients with PCS. Previous studies lacking control groups compared data pre- and post-HBO and found that HBO has a beneficial effect (5,6). However, a selection of prospective randomized trials did not prove the therapeutic effectiveness of HBO in PCS following mild TBI (7,8).

TBI is categorized into two phases: The primary insult and ensuing secondary reaction. A variable degree of irreversible

primary damage to the neurological tissue occurs at the onset of injury (9). Secondary pathologies of TBI include ischemia, edema, hypoxia and other biochemical and inflammatory processes (10,11). Local hypoxia and ischemia may lead to the initiation of neuronal cell death. The use of HBO to treat TBI is based on the fact that hypoxia may serve an important role in causing secondary injury (12).

Previous studies in animals have demonstrated that HBO may have beneficial effects on brain injury. HBO limits the growth of cerebral contusions (13), increases the contused hippocampus vascular density (14), decreases the extent of secondary cell death and reactive neuroinflammation (15), preserves mitochondrial integrity and inhibits the mitochondrial apoptotic pathway (16). As an adjunctive treatment for patients with TBI, HBO may reduce the risk of mortality and improve the final Glasgow Coma Scale score (17). However there is little evidence that the prognosis of survivors improves following HBO (18,19).

The present study conducted a systematic review and meta-analysis of the current literature to examine the benefit of HBO therapy in the treatment of patients with PCS. The current available clinical evidence was presented in order to provide a foundation for future research.

2. Methods

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (20) and was registered on the PROSPERO database (crd.york.ac.uk/PROSPERO; registration no. CRD 42016032620).

Study retrieval and screening. Studies were identified through by searching the Cochrane (cochranelibrary.com), EBSCOhost (search.ebscohost.com), Embase (embase.com/login), Ovid MEDLINE (ovidsp.ovid.com), PubMed (ncbi.nlm.nih.gov/pmc) and Web of Science (login.webofknowledge.com) databases. Database searches were limited to peer-reviewed scholarly journal articles published in English from inception up until the first week of 2016. Keywords, medical sub headings and an all fields search were conducted using the terms 'hyperbaric oxygenation' and 'post-concussion syndrome' to obtain articles meeting the eligibility criteria.

The results were analyzed independently by two reviewers. Three additional studies were identified from the reference lists of the retrieved studies, review articles and textbooks. All hits obtained with the search strategies were imported into EndNote version X7 (Clarivate Analytics, Philadelphia, PA, USA) and duplicates were subsequently removed.

The titles and abstracts of the remaining studies were screened by two reviewers independently to assess their eligibility. The full texts of potentially eligible studies were retrieved and assessed according to the inclusion criteria by the same two reviewers. Disagreements between the reviewers regarding the eligibility of titles/abstracts or full texts were resolved in a consensus meeting. In the case where consensus was not reached, a third reviewer was asked to make the final decision.

Eligibility criteria. The studies that satisfied all the following criteria were eligible for inclusion in the present review: i) Full-text articles published in a peer-reviewed scientific journal; ii) randomized controlled trials (RCTs) aimed at assessing the effectiveness of HBO in PCS; and iii) articles written in English. Exclusion criteria included studies that were not written in English, not RCTs or conducted in patients with mild brain injury who were not diagnosed with PCS.

Methodological quality assessment. The Cochrane Risk of Bias tool (21) was used to assess the methodological quality of the included studies in terms of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias.

Data extraction. The following data were extracted from the full texts of the studies included in the present review: Author, year published, study design, population, sample size, patient age and sex, intervention and comparison, outcome and outcome administered time. Data were extracted by one reviewer and reviewed a second time by a different reviewer to ensure accuracy.

Statistical analysis. Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration; ims.cochrane.org/revman) was used for data analysis. Pre- and post-intervention data were analyzed and compared. The weighted mean difference (MD) was pooled for continuous outcomes using the same measurement and the standardized mean difference (SMD) was calculated for continuous outcomes with different measurements. Statistical heterogeneity was detected using the Q statistic and I^2>50% indicated high heterogeneity. Using a 95% confidence interval (CI) a fixed effect model was used where there was no evidence of significant heterogeneity between studies and a random effects model when such heterogeneity was high. P<0.05 was considered to indicate a statistically significant difference.

3. Study selection and participants

Study selection and characteristics. A total of 126 articles were identified through database searching and 43 of these were screened following the removal of duplicates (Fig. 1). These included 13 comments and reviews (22-34), 9 letters to the editor and their matching responses (35-43), two conference abstracts (44,45), one paper on study design (2), one animal experiment (46) and one study on side effects (47). These studies were not RCTs and were therefore excluded. Concussion was not the focus of four of the studies screened (48-51) and an additional four studies (5,6,19,52) were not RCTs. Therefore following the exclusion of the aforementioned studies, eight RCTs (4,7,53-57) were suitable for inclusion in the current review (Fig. 1). Four of these (7,53-55) reported different aspects of the same study and another two (4,42) reported on the same trial; therefore these articles were evaluated together. A total of four articles were therefore used in the subsequent meta-analysis (4,8,55,56). Characteristics of the included studies are presented in Table I.

Participants. A total of 238 patients were enrolled in the studies included in the present review. The majority of these were members of the military service (4,8,55) apart from

Table I. Characteristics of the enrolled studies.

Authors (year)	Study design	Population	Sample size (n)	Mean age (years)	M/F (n)	Intervention and comparison	Outcome	Outcome administered time	(Refs.)
Miller *et al* (2015)	RCT	Military service members	72	31	69/3	HBO group, 1.5 ATA of 100% oxygen, 40x60 min sessions over 8 weeks; Sham group, room air pressurized to 1.2 ATA, 40x60 min sessions over 8 weeks; Standard care group, no supplemental chamber procedures	RPQ NSI PCL	Baseline; post-intervention	(8)
Cifu *et al* (2014)	RCT	Military service members	60	23	60/0	Sham air group, 10.5% oxygen (balance 89.5% nitrogen) at 2.0 ATA; 1.5-ATA oxygen group, 75% oxygen (balance 25% nitrogen) at 2.0 ATA; 2.0-ATA oxygen group, pure oxygen (0% nitrogen) at 2.0 ATA	RPQ PCL	Baseline; immediately post-intervention	(55)
Boussi-Gross *et al* (2013)	RCT	Patients with mild traumatic brain injury	56	44	24/32	HBO group, 100% oxygen at 1.5 ATA 40x60 min sessions over 2 months; Crossover group, a 2 month control period followed by HBO therapy	EQ-5D Cognitive Outcomes SPECT	Baseline; immediately post-intervention; post 2-month control period (crossover group)	(56)
Wolf *et al* (2012)	RCT	Military service members	50	28	48/2	HBO group, 2.4 ATA of 100% oxygen; Sham group, room air at 1.3 ATA Both 30x90 min sessions	PCL ImPACT	Baseline; each exposure interval; 6 weeks post-intervention	(4)

RCT, randomized controlled trial; HBO, hyperbaric oxygenation; ATA, atmospheres absolute; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; NSI, Neurobehavioral Symptom Inventory; PCL, Post-Traumatic Stress Disorder Checklist; ImPACT, Immediate Post-Concussion Assessment and Cognitive Testing; EQ-5D, EuroQoL Group's 5-dimension questionnaire; SPECT, Single-photon emission computed tomography.

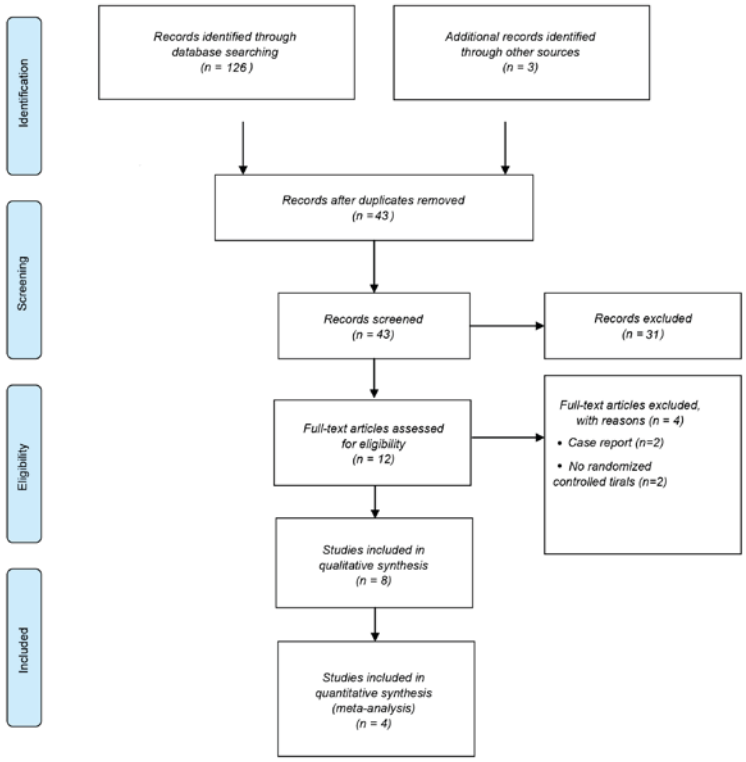

Figure 1. Review flowchart.

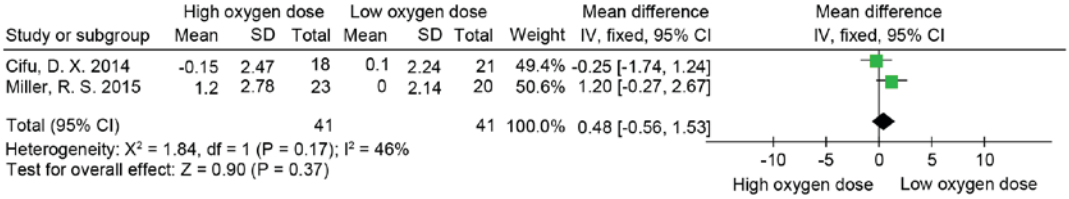

Figure 2. Rivermead Post-Concussion Symptoms Questionnaire-3 comparison between different oxygen dosage groups. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

the participants of one study, who were patients with mild, traumatic brain injury (56). The age range of all participants was 23-44 years and there were 201 males and 37 females.

Intervention. Trial designs varied among the studies included in the present review (Table I). A crossover control without a sham group was used in one study (56). Patients in the treatment group underwent 40 HBO sessions for 60 min with 100% oxygen at 1.5 atmospheres absolute (ATA). Patients in the crossover group underwent the same HBO therapy following a 2 month control period of no treatment. HBO and sham groups were used in two of the other studies (4,8) and one study also included a standard care group with no supplemental chamber procedures (8). In one study, patients in the HBO group underwent a series of 30 hyperbaric chamber compressions at 2.4 ATA with 100% oxygen, once each day for 90 min over an 8 week period, whereas participants in the sham group breathed air at 1.2-1.3 ATA (4). In the other study, patients in the HBO group underwent a series of 40 60 min hyperbaric chamber compressions at 1.5 ATA with 100% oxygen over 8 weeks and participants in the sham group breathed air at 1.2 ATA (8). In a study by Cifu *et al* (55), subjects breathed 1 of 3 pre-assigned oxygen fractions for 60 min, including 10.5% oxygen, 75% oxygen or 100% oxygen all at 2.0 ATA, resulting in an exposure to oxygen equivalent to breathing surface air, 100% oxygen at 1.5 ATA or 100% oxygen at 2.0 ATA, respectively.

4. Clinical outcomes

Rivermead post-concussion symptoms questionnaire (RPQ). RPQ (58) scores were measured in two of the trials included in the present review (8,55). The psychometric properties of the RPQ suggest that it is most appropriately scored and analyzed using two subscales. These subscales consist of items 1-3, which constitute the RPQ-3 score and the remaining 13 items constitute the RPQ-13 score (59,60). Following measurement of the individual doses of oxygen in partial pressures and concentration of oxygen multiplied by time for each treatment, the oxygen equivalent patients of the two studies were pooled into one group, thus generating two new groups: A high oxygen dose group and the low oxygen dose group. The difference in RPQ-3 (MD=0.48; 95% CI, -0.56-1.53; P>0.05; I^2=46%; Fig. 2), RPQ-13 (MD=0.91; 95% CI, -3.04-4.86; P>0.05; I^2=20%;

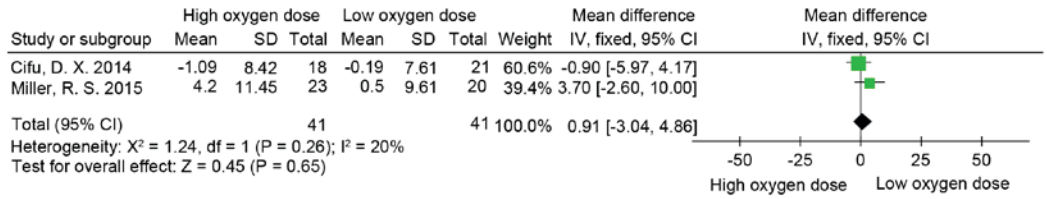

Figure 3. Rivermead Post-Concussion Symptoms Questionnaire-13 comparison between different oxygen dosage groups. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

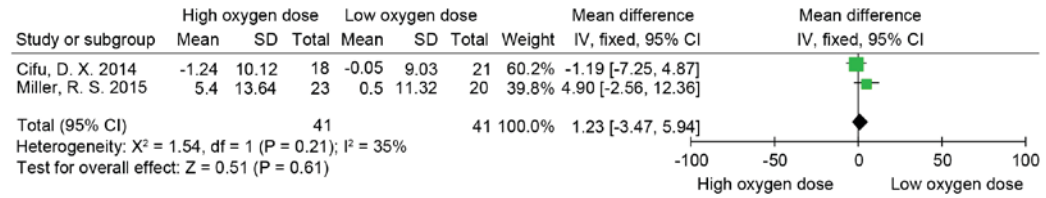

Figure 4. Rivermead Post-Concussion Symptoms Questionnaire-total comparison between different oxygen dosage groups. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

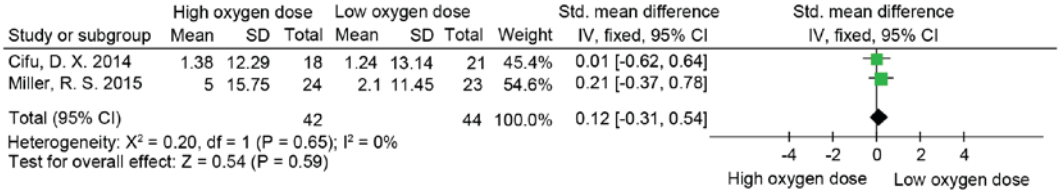

Figure 5. Post-traumatic stress disorder checklist comparison between different oxygen dosage groups. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

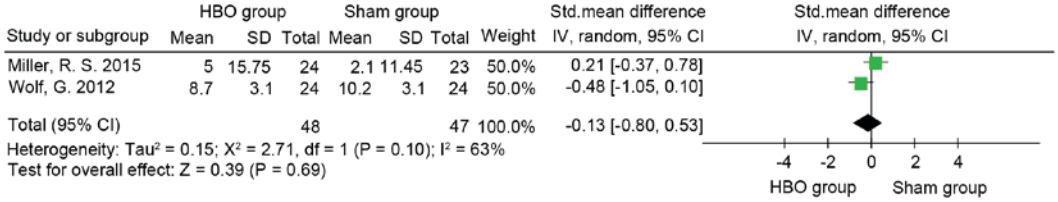

Figure 6. Post-traumatic stress disorder checklist comparison between HBO and sham groups. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom; HBO, hyperbaric oxygenation.

Fig. 3) and RPQ-total scores (MD=1.23; 95% CI, -3.47-5.94; P>0.05; I^2=35%; Fig. 4) was not significant between the low and high oxygen dose groups.

Post-Traumatic Stress Disorder Checklist (PCL). A total of 3 out of 4 studies included PCL in their results (4,8,55). Two (4,52) used the military version (60) and one (8) used the civilian version (61). The results indicated that the difference between the high and low oxygen dose groups (SMD=0.12; 95% CI, -0.31-0.54; P>0.05; I^2=0%; Fig. 5) and HBO and sham groups (SMD, -0.13; 95% CI, -0.8 to 0.53; P>0.05; I^2=63%; Fig. 6) was not significant.

Neurobehavioral symptom assessment. The neurobehavioral symptoms of participants were monitored in two trials (4,8) using the Neurobehavioral Symptom Inventory (NSI) (8,62) and Immediate Post-Concussion Assessment and Cognitive Testing (4,63), respectively. The difference between the neurobehavioral symptoms of subjects in the HBO and sham groups was not significant (SMD=-1; 95% CI, -2.58-0.58; P>0.05; I^2=92%; Fig. 7).

Health-related quality of life (QOL). Miller *et al* (8) demonstrated an improvement in health-related QOL outcomes, including physical functioning, bodily pain, social functioning and emotionality on the 36-Item Short Form Health Survey (SF-36) in the sham group compared with the HBO group and in the HBO group compared with the standard care group. QOL was evaluated in another trial using the EuroQuol five dimensions (EQ-5D) questionnaire (56). The EQ-5D questionnaire scores significantly improved following HBO therapy in the treated and crossover groups compared with the control group (P<0.05). However, no improvements were observed in the EQ-5D score in the crossover group following the control

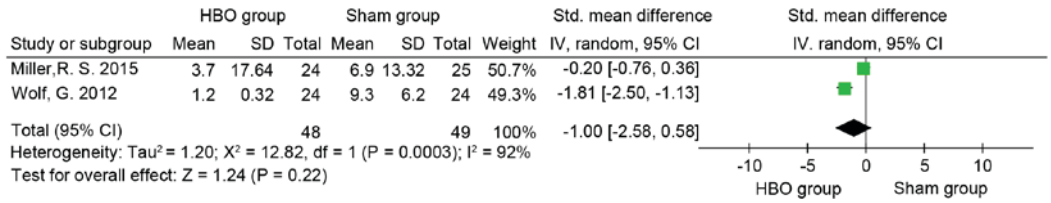

Figure 7. Neurobehavioral symptom comparison between HBO and sham groups. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom; HBO, hyperbaric oxygenation.

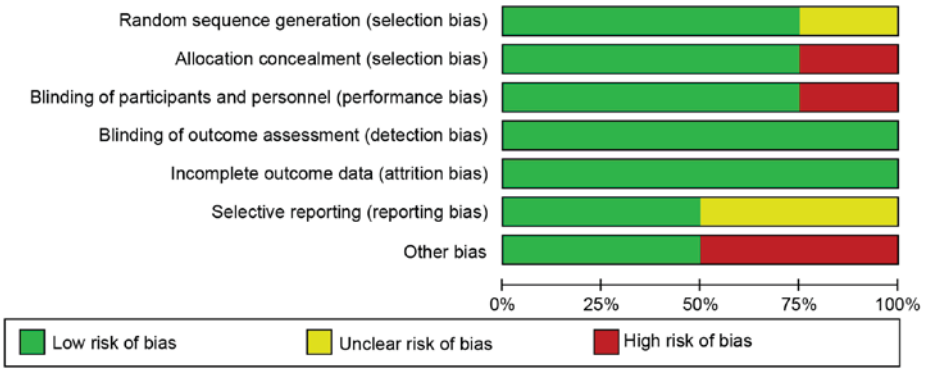

Figure 8. Risk-of-bias graph.

period. These results suggest that HBO therapy may improve QOL compared with the no supplemental chamber procedure, but not compared with the sham group. The standard deviation of SF-36 total score change was not available, thus a meta-analysis on QOL was not performed.

Cognitive function. There were insufficient data to conduct a meta-analysis on cognitive function. The crossover design study demonstrated significant improvements in cognitive function in the groups following HBO but no significant improvement following the control period (56). Single-photon emission computed tomography (SPECT) imaging also revealed elevated brain activity with cognitive improvements (56). Exposure to 1.5 or 2.0 ATA did not improve cognitive function compared with the sham air intervention in one study (7). Wolf *et al* (42) demonstrated that the difference in cognitive function between the sham and treatment groups undergoing HBO therapy at 2.4 ATA was not significant.

Quality and risk of bias. There was a low risk of bias in blinding outcome assessment and incomplete outcome data in the studies included in the present review (Fig. 8). However, the crossover study exhibited high risk regarding the blinding participants and personnel, as well as allocation concealment. A high risk of other bias was identified in two studies, including regarding the sham group as a control. The randomization method was unclear in 1 out of 4 studies. Therefore, the risk of bias among all studies was classed as medium due to selection, reporting and performance biases (Fig. 8).

5. Discussion

PCS is a term used to describe the complex and controversial physical, cognitive and emotional symptoms associated with mild brain injury. PCS persists for weeks or months in the majority of patients and <25% of patients may experience prolonged PCS in which symptoms last for >6 months (64). These patients are at high risk of emotional and cognitive dysfunction in which they may be unable to perform ordinary daily activities and maintain work responsibilities, as well as normal social relationships (65,66). Currently, there is limited evidence that multifaceted rehabilitation programs that include psychotherapy improve the management of persistent symptoms in PCS (67). Based on previous studies investigating other neurological conditions, it has been suggested that HBO therapy may be a potential treatment for chronic PCS (5,6,52).

The results of the present systematic review identified no improvement in RPQ score or symptoms of PCS between low and high oxygen dose groups and no significant difference in the improvement of neurobehavioral symptoms between HBO and sham groups. Thus, there is no evidence that HBO therapy is effective at treating patients with PCS. However, HBO therapy is a combination of increased pressure and increased pressure of oxygen above ambient atmospheric pressure and the sham designs used in the studies included in the present review may not have tested an extensive enough range of pressurized air doses (37,57).

The effects of air pressure have been investigated since the early 20th century; however, they have been more actively studied since the 1990s. The majority of studies performed so far have been cell culture experiments (57). A follow-up study by Mulkey *et al* (68) suggests that neuronal barosensitivity occurs at pressures of 100 mmHg (1.13 ATA). Furthermore, it has been demonstrated that even a small increase in partial pressure to 1.05 ATA at an altitude of 402 m below sea level may induce noticeable physiological effects, such as improved pulmonary function and blood oxygen saturation (69-71). A room air pressure of 1.2 or 1.3 ATA may not be appropriate

for sham controls, as this may lead to significant increases in tissue oxygenation (72). Thus, the use of 21% oxygen at 1.14-1.5 ATA in for sham controls in clinical trials as an alternative to observation or crossover controls may lead to false acceptance of the null hypothesis, due to the biological activity that occurs under these conditions (29). Consequently, studies that included a sham group were identified as having high bias (4,7,8,55). The minimum pressure at which patients sense an increase in air pressure is 1.3 ATA. Controlled experiments testing the effects of HBO therapy must therefore ensure that pressure and oxygen concentrations are not above base levels in the control groups to meet the true definition of a sham (73). However, this may result in inherent ethical and logistic difficulties in handling the sham control in HBO trials.

Objective and precise assessment methods are another challenge in evaluating the efficacy of HBO therapy in patients with PCS. To the best of our knowledge, validated outcome measures for intervention trials in PCS have not yet been established. In the majority of the studies included in the present review, outcomes were evaluated using RPQ, PCL or NSI. All of these assessments are well established; however, they are all subjective performance evaluations (58,60-62). The RPQ has several limitations in its implementation and ability to accurately reflect test-taker experience (74). The interpretation and accuracy of the RPQ and other methods varies widely due to self-administration and the confounding variables involved due to its sensitivity to covariates, including subjective patient memory, social desirability, stress, personality factors and the willingness of patients to reveal problems (74). The studies included in the present review relied on self-administration assessments, which is a limitation. SPECT imaging was used in one randomized, crossover controlled trial and revealed elevated brain activity with cognitive improvements following HBO therapy in the treated and crossover groups (56). This is consistent with the results of previous studies (5,6). Although the use of SPECT imaging may not be sensitive enough to detect abnormalities in patients with PCS, it is an objective assessment method that may provide evidence supporting the use of HBO or sham interventions and allows a greater refinement of HBO treatment for patients with PCS.

A study of HBO therapy used to treat sub-acute moderate to severe TBI at 2.0 ATA reported a 9% seizure rate (75). However, serious side effects from HBO therapy are rare in patients with chronic and mild TBI and a previous study demonstrated that patients with TBI treated with HBO do not experience any marked side effects (76). Two trials in the current study reported that adverse events occurred during HBO therapy, which were equally distributed between the HBO and sham groups (8,47) included in the present review. Serious adverse events, including pulmonary barotraumas, pulmonary edema or seizure were not observed.

There are several differences between blast-related and sports-related PCS. Patients with blast mild TBI have usually experienced two episodes of head trauma, often within sec of each other. The magnitude of head acceleration is stronger than that of a sports-related concussion and the entire body is exposed to the blast. Consequently, blast TBI is caused by multiple, interwoven mechanisms of systemic, local and cerebral responses to blast exposure (77). The majority of patients included in the present review were from the military, thus, the results are not representative of patients diagnosed with sports-related concussion.

Previous studies have demonstrated that there is an optimal therapeutic time frame for HBO treatment in neonatal rats with hypoxic-ischemic brain damage (78-80). However, to the best of our knowledge, the optimal timing of treatment for patients with brain injury remains unknown. Efrati and Ben-Jacob (23) suggested that HBO therapy may begin either at the degenerative or regenerative stages and is usually safe 1 month following acute injury. Subset analysis of isolated mild TBI demonstrated a trend toward harm from HBO at 2.4 ATA, suggesting that HBO at 2.4 ATA may actually have a negative impact on isolated mild TBI symptoms (81), however, the optimal effective doses of pressure and oxygen concentration in HBO therapy remain unclear, as does the optimal duration of treatment. The majority of the results of the studies included in the present review were obtained following 30-40 sessions of HBO therapy. It is hypothesized that additional sessions of HBO therapy may be beneficial (43) however, to the best of our knowledge, no data are available on the upper time limit at which no further improvements occur. The long-term effects of HBO therapy are not well studied. In the studies included in the current review, the time point for outcome assessment was usually <1 week following completion of treatment. One previous study identified that treating blast-related PCS 3 months following compression had no significant effect (53). Thus, further studies are required to develop understanding of the optimal number, duration and long-term effects of treatment sessions and the optimum time frame following injury onset for initiating HBO therapy.

Case reports and phase I clinical trials have demonstrated that HBO is an effective therapy for correctly diagnosed PCS (5,6) however, the results of RCTs included in the current review were not consistent with this. HBO therapy may improve the symptoms of patients with increased levels of oxygen concentration and pressure. The results of the current meta-analysis indicated that increased doses of oxygen had no effect on PCS. The efficacy of pressurization remains elusive, as the symptoms of patients in the HBO and sham groups were improved with no difference in improvements observed between them. It is therefore essential to develop a sham that controls for pressurization or oxygen concentration separately in RCTs.

Although it remains unknown whether the symptoms of PCS improve following HBO therapy, it has been demonstrated that HBO therapy does not cause any serious side effects; thus, it has been recommended that patients with PCS should undergo HBO therapy, until future studies are completed. However, it should be noted that HBO treatment is costly and potentially dangerous thus, its use must be evidence-based (82). The use of genuine sham controls in studies on HBO therapy is not feasible or cost effective and the optimal therapeutic window and oxygen dose of HBO therapy remain unknown. Therefore future studies should be conducted on a large scale or in cohorts to produce more useful results. The approval of HBO therapy on a tentative basis would allow for studies to be conducted on a large patient population.

There were several limitations of the current meta-analysis. Although a comprehensive search of six databases was conducted, only four studies consisting of 238 patients in total were included in the present systematic review. The small

number of included studies limited the statistical power of detection. Additionally, the sample set of patients used is not representative of patients with sport-related PCS due to the small number of studies included, which primarily included members of the military that had experienced blast-induced PCS. A comparison of all groups was not conducted due to the heterogeneity between different trials. In addition, the study design of the sham group may lead to high bias. Therefore, more rigorous reviews are required to assess the effects and safety of HBO therapy in patients with PCS.

In conclusion, the present systematic review demonstrated that HBO therapy was not associated with significant improvements in patients with PCS. Large scale observation or cohort studies are required to provide information for the design and execution of a large clinical trial consisting of proper treatment, control and sham groups. This future trial may subsequently provide the evidence required for the efficacy of HBO therapy in the treatment of patients with PCS.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author's contributions

ToW made substantial contributions to the conception and design of the study. YD and XHH searched and analyzed the data independently. In the case where consensus was not reached, TaW was asked to make the final decision and interpret the data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare no conflicts of interest.

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