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The Effects of Hyperbaric Oxygen Therapy on Mild Traumatic Brain Injury and Post-Concussion Syndrome: A Qualitative Research Analysis

Introduction

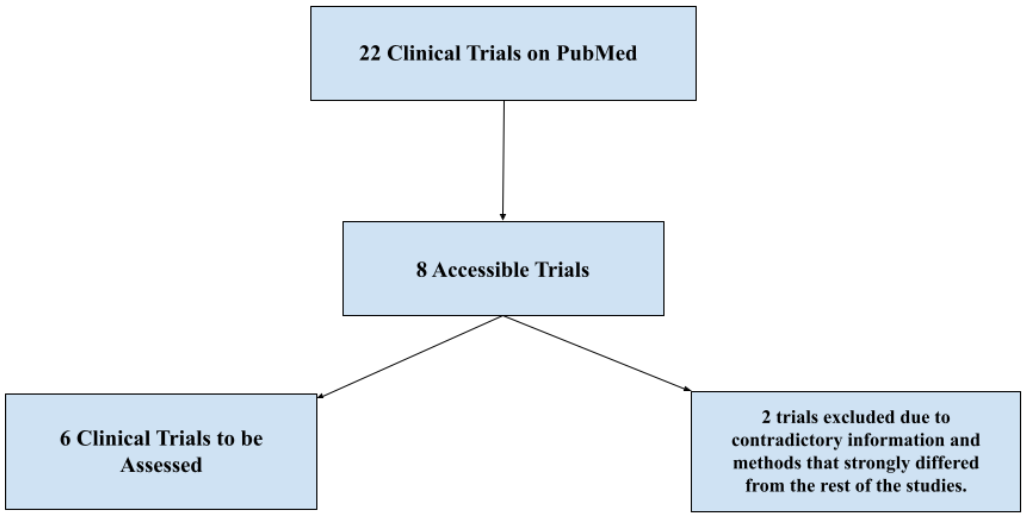
In the United States alone, mild traumatic brain injury (mTBI) accounts for about 80% of all brain injuries, coming in at 4.1 million mTBI cases and 61,000 deaths related to TBI per year. Especially for the service men and women who incur many of these brain injuries, TBI has become an alarming public health concern. Around 15% of mTBI cases are also diagnosed with post-concussion syndrome (PCS). To date, there are little to no effective treatment options that help symptoms in both mTBI and PCS. Hyperbaric oxygen therapy (HBOT) could be a potential candidate to help suppress symptoms of mTBI and PCS through the hypothesis of the treatment helping oxygenate the blood and tissue of the brain, therefore creating supraphysiological levels. Another theory of the treatment is that HBOT helps revive a patient's damaged neurons through metabolic pathways to function normally. Oxygen toxicity is a severe side effect of hyperbaric oxygen treatments, therefore to reduce the odds of this side effect, all clinical trials included are either 60 minutes per treatment or give air breaks during treatment. Studies have been done to evaluate the effectiveness of HBOT on TBI and PCS, but the results in the studies are skewed, therefore it is important to assess clinical trials to evaluate the effectiveness of HBOT on mTBI and PCS. Evaluating this will also give future research an idea of what needs to be focused on.

Objectives

- Evaluate different clinical trials to evaluate effectiveness of hyperbaric oxygen therapy on mTBI and PCS
- Determine what research needs to be conducted to help evaluate the efficiency of HBOT in mTBI and PCS

Methods

Since mild traumatic brain injury and post-concussion syndrome are major public health concerns, I decided to carefully set parameters, inclusions, and variables that would be sufficient in my analysis to better help the population suffering from mTBI. Using an advanced search on Pubmed using specific keywords (hyperbaric oxygen therapy, post concussion syndrome, mild traumatic brain injury, concussion, and clinical trial), I found 22 clinical trials as potential candidates. Out of the 22 clinical trials, I only had access to 8 of the articles. With that, two trials were excluded due to contradictory information and incompatibility with the inclusion criteria that was placed compared to other clinical trials, leaving 6 articles to be compared and analysed. Subjects included were between the age range 18-65, had been diagnosed with a mild traumatic brain injury within the last 3 months and/or expressed symptoms of postconcussion syndrome, and were cited as being stable on psychiatric medication for at least 1 month (if applicable). The variables of the studies (ATA) could range from 1.2 ATA (sham-air) to 3.0 ATA. The amount of time that subjects spent in the chamber varied from 60-90 minutes, but stayed consistent throughout each study, and if the amount of time exceeded 60 minutes in the chamber, oxygen breaks had to be given to reduce oxygen toxicity. The 6 available clinical trials were then organized into a table that includes subject qualifications, size of the studies, duration, methods of the studies, type of test run, scales used to track participants' progress, and the results of each study.



*This chart serves as a visual diagram to explain how clinical trials were selected and assessed to avoid biases, specifically selection bias.

Results

	Subject Qualifications	Methods	Size	Scales Used	Results
(Wolf et al.)	- neurological confirmed mTBI within the range of 3-71 months prior to treatment was necessary - age ranged from 20-51	- double-blind, randomized, sham-controlled trial (paired t-test was used) - tested before and after treatment, and measured in increments of 5 chamber sessions - groups underwent 30 sessions, 90 minutes (10 minute air-breaks every 30 minutes), at either 2.4 ATA or sham-air over a six week period	HBOT Group: n=25 Sham Group: n=25	Used Post-traumatic Disorder Checklist-Military Version (PCL-M) and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) $p < 0.01$ for both PCL-M and ImPACT to be significant.	No significant differences were found between the HBOT and Sham groups. Sham Group: 10 ImPACT symptom scores differed from the beginning of the study to the post-testing HBOT Group: 2 ImPACT scores significantly changed. No PCL-M scores were significant in either group.

(Miller et al.)	- must have had ongoing symptoms for at least 4 months, and be diagnosed with a mTBI - had to be at least 18 years old and serve in the military	- double-blind, sham-controlled trial (used paired t-test) - subjects were assessed before treatment, at the midpoint, and after completing treatment - groups underwent 40 treatments at either 1.5 ATA or 1.2 ATA (sham) for 60 minutes over a ten week period - Standard Care Group practiced routine PCS procedures created by the DoD	HBOT Group: n=24 Sham Group: n=25 Standard Care Group: n=23	Primary Outcome Measures: Rivermead Post-Concussion Symptom Questionnaire (RPQ-3) Secondary Outcome Measure: Neurobehavioral Symptom Inventory Score (NSI) A change of 2 points is considered statistically significant on the RPQ-3 scale. $p < 0.05$ is statistically significant.	Primary Outcome: None of the three groups scored a change of 2 points on the RPQ-3 scale, as all groups showed slight improvements in symptoms. $p = 0.24$; no significance Secondary Outcomes: A slight worsening was shown in the standard care group from the baseline on the NSI scale. Improvement was shown with the HBOT group, but not enough to be significant. $p = 0.49$; no significance
(Cifu et al.)	- subjects must have shown PCS symptoms for at least 3 months with the injury occurring in the past 3 years confirmed by the DoD standards of mTBI - participants are at least 18 and serving in the military	- double-blind, randomized, sham-controlled trial (used one-way ANOVA test) - 3 groups (surface air, 1.5 ATA, 2.0 ATA) underwent 40 treatments over a ten week period for 60 minutes each - subjects were assessed before starting treatment and after treatment	Surface Air Group: n=21 1.5 ATA Group: n=18 2.0 ATA Group: n=21	Primary Outcome: Rivermead Post-Concussion Symptom Questionnaire (RPQ) specifically from RPQ-3 and RPQ-13 Secondary Outcome: Post-traumatic Stress Disorder Checklist-Military Version (PCL-M) $p < 0.05$ is considered statistically significant for both tests	Primary Outcome: 1.5 ATA showed worsening symptoms in light sensitivity; 2.0 ATA improved in noise sensitivity and frustration/impatience. Secondary Outcome: Surface Air Group and 1.5 ATA improved in being alert/watchful; 2.0 ATA showed improvement in being upset when reminded of past events that were stressful and being alert/watchful. 2.0 ATA Group improved in the PCL-M tests by 3.77 points, but not enough to be statistically significant, therefore no groups were found to be statistically significant.
(P. Harch et al.)	- subjects had to have a mTBI that was at least 6 months old, score at least 22 on the Neurobehavioral Symptom Inventory - subjects were 18-65 years old	- double-blind, randomized trial that crossed over sham group to treatment after study (two sample t-test was used) - 40 sessions for 60 minutes, 5 days/week for 2 months at either 1.5 ATA or sham air - subjects were assessed before starting treatment and after treatment	Control Group: n=27 HBOT Group: n=25	Primary Outcomes: NSI and Working Memory Index Secondary Outcomes: Automated Neuropsychological Assessment Metrics, Memory Index, Information Process Speed Index, WAIS-IV, Hamilton Depression Scale, Hamilton Anxiety Scale, PCL-M, Pittsburgh Sleep Quality Index, Quality of Life after Brain Injury compared to Control, Benton Visual	Primary Outcomes: NSI and Working Memory index experienced a 26.3 decrease within the HBOT Group compared to a 2.5 decrease in the Control Group. $p = 0.0001$; statistically significant Secondary Outcomes: Eight of the 14 outcomes improved significantly. Results favor hyperbaric oxygen therapy to the control group.

				Retention Test, RAVLT $p < 0.05$ is statistically significant for both groups	
(P. G. Harch et al. 1)	- subjects had a mTBI that was at least one year old and have a diagnosis of PCS - subjects were 18-65 years old	- this study had no control group; everyone receives treatment - subjects underwent 40 sessions twice a day for 5 days a week at 1.5 ATA for 30 days - tested subjects before and after treatment	HBOT Group: n=15	Symptom and Physical Exam: Participants listed severity of symptoms they were experiencing and answered the P.I.'s questionnaire. Psychometric/Emotional Testing: Combat Experience Scale, Green World Memory Test, Percent Back to Normal Rating, RPQ, PCL-M, WAIS-IV, WASI, Tes of Variables of Attention, Stroop Test, Finger Tapping Test, Grooved Pegboard, WMS-IV, Rivermead Paragraph Memory, Perceived Quality of Life, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7 SPECT: Used SPECT to measure blood flow of the brain and for mapping analysis. $p < 0.05$ to be statistically significant.	Symptoms and Physical Exams: 12 of the 15 subjects improved symptoms on their severity list; 11 out of 15 reported improvement on the P.I. Questionnaire. Psychometric/Emotional Testing: Working Memory ($p = 0.003$) and Stroop Tests ($p < 0.001$) were the most significant results. WMS-IV also significantly improved ($p = 0.026$). All eight emotional tests showed a significant outcome, PCL-M most significant ($p < 0.001$). Symptoms of PCS and PTSD improved drastically. SPECT: In the right hemisphere, there was a significant increase in 60, 90, 150° gray matter ROIs. In the left hemisphere, there was a significant increase of 30 and 150° gray matter ROIs and 60° white ROIs. 50 significant clusters in mapping analysis were considered significant.
(Boussi-Gross et al.)	- subjects must have incurred a mTBI within the past 1-5 years with PCS, but brain damage wasn't seen in CT or MRI scan - subjects must be at least 18 years old to participate	- double-blind, randomized trial - subjects underwent 40 sessions at 60 minutes each 5 days a week for 2 months at either 1.5 ATA or 1.2 ATA - HBOT Group was evaluated at baseline and 2 months after treatment - Crossover Group was evaluated at baseline, 2 months after control period, then 2 months after real treatment	HBOT Group: n=32 Crossover Group: n=24	Mindstream Testing: This category was made up of testing memory, executive function, attention, and information processing speed. Quality of Life Questionnaire: This category was made up of the EQ-5D test and the EQ-VAS test. SPECT: SPECT brain imaging was used to evaluate the changes in brain activity. $p < 0.05$ is statistically significant in all categories.	Mindstream Testing: The HBOT Group significantly improved in all categories, and so did the Crossover Group after treatment. Quality of Life Questionnaire: Both the HBOT and Crossover Group (after treatment) both improved drastically in the EQ-5D and EQ-VAS tests. SPECT: SPECT showed an increase in perfusion in both the Crossover Group (after treatment) and the HBOT Group compared to the baseline imaging.

Throughout this qualitative data analysis with the available clinical trials to examine, the results of hyperbaric oxygen therapy suppressing symptoms of mTBI and PCS remain inconclusive. From the clinical trials (P. G. Harch et al. 1) and (Boussi-Gross et al.), the hypothesis of hyperbaric oxygen treatment helping oxygenate the blood and tissue in the brain may be deemed true because of the significant findings from the SPECT brain imaging from both studies. In (P. G. Harch et al. 1) specifically, the blood flow in the brain was significantly better after the 40 HBOT treatments compared to the baseline SPECT imaging.

Conclusions/Limitations

In the three groups that had insignificant findings of hyperbaric oxygen therapy, the studies claimed that the placebo effect may be skewing the results. Specifically, in (Wolf et al.), 10 symptom scores differed in the Sham Group compared to only 2 symptom scores that significantly differed in the treatment group. This could also be due to the change in the participants' schedules, as their work hours were reduced for treatment purposes. Another variable that could affect the results of the clinical trials are the tests that were chosen by each research study. (Wolf et al.), (Miller et al.), and (Cifu et al.) all have either a primary and secondary test measure, or only two tests run. Yet in (P. Harch et al.), (P. G. Harch et al. 1), and (Boussi-Gross et al.), they all have several categories of different tests that are run that explore symptoms, psychometric analysis, quality of life, and brain imaging. Because a larger number of tests were run in these clinical trials, they may be more accurate for overall analysis.

Future Direction

After examining six different clinical trials of the effects that hyperbaric oxygen therapy has on mTBI and PCS, the results still remain inconclusive, as the findings are split. Future clinical trials need to be done on this topic to fully evaluate whether this treatment is probable. These trials should include many different tests that deal with symptom scoring, psychometric and emotional testing, and SPECT or another type of brain imaging tool. Also, research may need to

be done on the effects that HBOT has on severe traumatic brain injury, as there are few clinical trials that focus on severe cases and the results may differ from mTBI findings.

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