RESEARCH ARTICLE

Hyperbaric oxygen therapy ameliorates the symptoms of post-concussion syndrome by inhibiting MMP-9 activity: a randomized controlled trial in Indonesia [version 1; peer review: 2 not approved]

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Abstract

Introduction: Post-concussion syndrome is common in young adults and can greatly interfere with the quality of daily life. It has a wide range of symptoms that require prompt and well-targeted treatment to avoid further brain impairment. Hyperbaric oxygen therapy (HBOT) is a promising regenerative treatment option for these patients to help prevent the progression of post-concussion syndrome. This study aims to determine whether HBOT accelerates the healing process and reduces symptoms in patients with post-concussion syndrome.

Methods: 20 patients with post-concussion syndrome participated in this randomized controlled trial study. After receiving standard mild traumatic brain injury treatment in accordance with the Advanced Trauma Life Support guidelines, the patients were divided into HBOT and control groups. Matrix metalloproteinase 9 (MMP-9)

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levels and Rivermead Post-Concussion Symptoms Questionnaire (RPQ) scores were used to compare the two groups (before HBOT & after 1st, 3rd, and 5th week).

Results: The study sample was predominantly male (65%) with an average age of 60 years old. HBOT reduced serum MMP-9 levels by nearly 20 ng/mL ($p < 0.001$) compared with the control treatment. The efficacy of HBOT was also reflected in the RPQ scores, which were significantly lower in the HBOT group than the control group (before HBOT & after 1st, 3rd, 5th week) (-3.80 on RPQ-3, $p = p < 0.001$; -16.20 on RPQ-13, $p = p < 0.001$).

Conclusion: HBOT ameliorated the symptoms associated with post-concussion syndrome through a mechanism that involves MMP-9 activity. The accelerated recovery observed in the present study supports the use of HBOT to treat post-concussion syndrome and potentially other forms of traumatic brain injury.

Keywords

Hyperbaric oxygen therapy; Traumatic brain injury; Post-concussion syndrome; Rivermead Post-Concussion Symptoms Questionnaire; Matrix metalloproteinase 9; Randomized controlled trial.

Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Head injury is the leading cause of death and disability among young adults.¹ In Indonesia, head injuries account for almost half of all deaths caused by trauma.²⁻⁴ The symptoms of head injury range from mild to severe depending on the extent of brain damage.⁵ Patients with head injuries often experience considerable cognitive, behavioral, and communication impairment.⁶ These patients deserve prompt, effective treatments that are not only lifesaving but also preserve their brain function.

Hyperbaric oxygen therapy (HBOT) involves the inhalation of 100% oxygen at a higher pressure than the atmospheric standard. Patients inhale 100% oxygen, and pressure increases gradually to 2-3 absolute atmosphere (ATA).⁷⁻¹⁰ HBOT has become popular in the field of neurology because it inhibits apoptosis, suppresses inflammation, and protects the integrity of the blood-brain barrier (BBB), in addition to stimulating angiogenesis and neurogenesis. The neuroprotective effects of HBOT are most effective during the acute phase, which is the first 24 hours post-head injury.¹¹

The anti-neuroinflammatory properties of HBOT are at least partially exerted by suppressing matrix metalloproteinase 9 (MMP-9) expression.¹² MMP-9 is a Zn-dependent endopeptidase enzyme that maintains and remodels the extracellular matrix (ECM). MMP-9 is produced by microglia, neurons, oligodendrocytes, astrocytes, and the vascular endothelium.¹³ In chronic brain injury, HBOT increases cerebral blood flow, improves any related neuropsychological disorders, and promotes neurophysiological and electrophysiological recovery.¹⁴ As such, this therapy improves the quality of life in patients with post-concussion syndrome and prevents its progression to more advanced stages.¹⁵ Taken together, these data suggest that HBOT represents a promising therapeutic modality for various forms of head injury.

The persistence of symptoms associated with mild traumatic brain injury (TBI) is referred to as post-concussion syndrome. The majority of patients with post-concussion syndrome recover within three to six months.¹⁶ In most clinical trials on the survey-based, patient progress was evaluated by neuropsychological examination such as the Rivermead Post-Concussion Symptoms Questionnaire (RPQ). The RPQ is one of the most commonly used instruments for determining the severity of the symptoms caused by mild to moderate TBI. Individual item scores reflect the presence and severity of post-concussion symptoms that overlap with a wide range of conditions (e.g., pain, fatigue, and mental health conditions including depression). The RPQ is divided into two groups; RPQ-3 and RPQ-13. RPQ-3 consists of three initial symptoms, such as headaches, feelings of dizziness, nausea and/or vomiting. The RPQ-13 is a progression of these initial symptoms, such as noise sensitivity, sleep disturbance, fatigue, feeling irritable, feeling depressed or impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness.¹⁷

Questionnaires are repeatedly administered to monitor the patient's progress over time and promptly identify changes in the severity of symptoms. The recovery process usually requires three to six months of conservative treatment to resolve the symptoms.¹⁸

However, these conservative treatments are slow and sometimes ineffective, leaving patients with life-long symptoms ranging from headaches to impaired cognitive function. Therefore, the present study aims to determine whether and how HBOT accelerates post-concussion syndrome recovery by analyzing RPQ scores and MMP-9 levels, respectively. We hypothesize that HBOT can improve post-concussion symptoms by decreasing MMP-9 levels in patients with TBI undergoing HBOT compared with traditional therapeutic approaches.

Methods

Study design

This study used a randomized controlled trial design to assess levels of MMP-9 and Rivermead Post-Concussion Symptoms Questionnaire (RPQ) scores at pre-treatment (baseline) and post-treatment at weeks one, three, and five.

Ethical approval

The study was conducted after obtaining approval from the research ethics committee of Prof. Dr. R. D. Kandou Hospital, Manado (Code number: 125/EC/KEPK-KANDOU/XII/2020). This study was registered with the Research Registry with a registration number no. 6465 on January 17, 2021. Written informed consent was obtained from all the participants. The work was carried out in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.^{19,20}

Population and sample

This study included 20 patients with mild TBI. The patients were randomly divided according to treatment into a control group and an experimental group. The experimental group received HBOT in addition to the Advanced Trauma Life Support (ATLS) protocol while the control group only received the latter. In accordance with randomized controlled trial

design, the patients in the control group were so selected because they refused to receive HBOT. The study was carried out at Dr. R. D. Kandou Hospital, Manado, North Sulawesi, Indonesia.

Procedure

All patients received standard mild TBI treatment according to the ATLS protocol including head CT scans using computed tomography SOMATOM Scope (Siemens Healthineers AG, Erlangen, Germany) to identify any brain abnormalities. The HBOT group also received 60-minute HBOT sessions, breathing in 100% oxygen at 2-3 ATA, three times during this study at weeks one, three, and five.²¹

RPQ score

Items in the questionnaires are divided into two groups. The first group (RPQ-3) consists of three items and the second group (RPQ-13) consists of 13 subsequent items.^{17,18,22} The total score for the RPQ-3 items range from 0-12 and reflect the baseline symptom pool of post-concussion symptoms. A higher RPQ-3 score requires reassessment and close monitoring.²³

MMP-9 measurements

Prior to initiating treatment in both groups, the RPQ was administered, blood samples were collected for serum MMP-9 assays, and head CT scans were performed to identify any brain abnormalities such as subarachnoid hemorrhage (SAH), epidural hematoma (EDH), subdural hemorrhage (SDH), and intracerebral hemorrhage (ICH). MMP-9 levels were measured in the Biomolecular and Immunology Laboratory of the Faculty of Medicine at Sam Ratulangi University in Manado, Indonesia after every HBOT session for both the HBOT and control groups. At the end of week 1, 3, and 5, all patients were reevaluated for serum MMP-9 levels and RPQ scores. An enzyme-linked immunosorbent assay (ELISA) was used to quantify MMP-9 levels in ng/mL, as described in the MMP9 Human ELISA Kit protocol (Invitrogen Corporation, Carlsbad, CA, USA), catalog number BMS2016-2.^{9,21,24}

Statistical analysis

Microsoft Excel was used for data entry and **R Statistical Software version 3.6.3**²⁵ was used for all statistical analyses. For the categorical variables, frequency tables were used to assess distributions. Both center and dispersion values were calculated according to the type of variable as was the normality of the distribution for numeric variables. Normally distributed numeric variables are presented as means and standard deviations (SD). If the distribution is abnormal, median values and interquartile ranges (IQR) are given. Differences for each variable according to the treatment group (HBOT vs control) were analyzed using the t-test for numerical variables and the chi-square or Fisher's exact test for categorical variables. Changes in serum MMP-9 levels in the treatment group according to the time of examination were visually evaluated using graphs and linear mixed model analysis with random intercept; these analysis measurements were repeated for each study subject. The effects of HBOT on serum MMP-9 levels and RPQ scores were evaluated using linear regression models. The modeling results are reported as changes in the outcome value for each unit increase in the independent variable, lower and upper limits of the 95% confidence interval (CI), and p-values, which were considered statistically significant below 0.05.

Results

Patient characteristics including age, sex, and the presence of intracranial bleeding are presented in **Table 1**. The average patient age was 39 years and this was not significantly different between the HBOT and control groups. The male-to-female ratio was approximately 6.5: 3.5. Intracranial bleeding was found in over half of the cases and these were equally distributed between the HBOT and control groups. No patient dropped out during the 6-week study period.

Serum MMP-9 levels and RPQ scores

Table 2 displays the MMP-9 levels and RPQ scores at different measurement time points. The two patient groups had different MMP-9 serum levels even before treatment was initiated; however, this difference was not statistically significant. While both groups experienced decreases in MMP-9 levels during the course of this study, the reduction in the HBOT group was significantly greater than in the control group (40.6 ng/mL vs 21.7 ng/mL; $p < 0.001$). Therefore, even though the control group had higher MMP-9 levels at baseline, this was compensated for by the highly significant endpoint difference (the difference between both scores (delta) after five weeks).

RPQ scores did not differ between the two study groups at baseline. However, by the end of week five, patients receiving HBOT had marked improvements in their RPQ scores compared with controls (mean 3.1 vs 6.5 for RPQ-3, 14.2 vs 29.6 for RPQ-13; both p -values < 0.001). As a result, the delta scores from baseline to week five in the HBOT group were higher compared with the control group (-8.0 vs -4.2 for RPQ-3, -23.4 vs -7.2 for RPQ-13; both p -values < 0.001).

Table 1. Patient characteristics.

Characteristics	Total (N = 20)	Control (n = 10)	HBOT (n = 10)	P ^a
Age ($\mu \pm SD$)	38.9 $\pm$ 15.1	38.0 $\pm$ 15.0	39.7 $\pm$ 16.0	0.809
Sex				
Male	13 (65)	7 (30)	6 (60)	1.000
Female	7 (35)	3 (30)	4 (40)	
Intracranial bleeding				
Negative	6 (30)	3 (30)	3 (30)	1.000
Positive				
SAH	5 (25)	2 (20)	3 (30)	
EDH	3 (15)	1 (10)	2 (20)	
SDH	1 (5)	1 (10)	0 (0)	
ICH	5 (25)	3 (30)	2 (20)	

Note: Data were successfully collected from twenty mild traumatic brain injury patients who participated in the study. The average age of these patients was 40 years but with quite a large variation (SD 15 years; Table 1). There was no significant difference in the ages of patients in the HBOT group compared to controls. The male-to-female ratio was approximately 6.5: 3.5 and the ratio was relatively unchanged when stratified according to the HBOT vs control group. Overall, patient characteristics in both groups were relatively similar. This is important to consider as the allocation of treatments in the study was not completely random. The absence of difference between both groups suggests that selection bias related to age, sex, or location of intracranial hemorrhage might be excluded. Another positive thing that supports the fairly even distribution of patients in the two study groups (thereby minimizing the possibility of selection bias that might be feared due to the allocation of treatment without randomization) is shown in Table 5.2. RPQ scores in the treatment group did not differ from the control group at baseline.

Abbreviations: SD = standard deviation, HBOT = hyperbaric oxygen therapy, SAH = subarachnoid hemorrhage, EDH = epidural hematoma, SDH = subdural hemorrhage, ICH = intracerebral hemorrhage.

^at-test for numeric variables, Fisher's exact test for categorical variables.

Figure 1 illustrates the changes in serum MMP-9 levels in both groups at four different time points. MMP-9 levels in the HBOT group are consistently lower and decline notably after two weeks compared with the control group. Figure 2 shows that the patients receiving HBOT had overall lower MMP-9 levels than those in the control group. Similarly, Figure 3 depicts the declining MMP-9 concentration in both groups over time and highlights that HBOT causes MMP-9 values to plummet within four weeks of initiating post-injury treatment compared with controls.

Regression analysis using a linear mixed model revealed that changes in MMP-9 level depended on the interaction between both groups (HBOT vs control) and time (Figure 4). The p-values for the group, time, and the interaction of both variables were highly statistically significant ($p < 0.001$). There was a decrease in MMP-9 concentration in both groups over time, however, this decline was accelerated in the HBOT group compared with controls.

Effects of HBOT on serum MMP-9 levels and RPQ scores

Table 3 presents the regression analysis of the relationship between the outcome variables (MMP-9 concentration and RPQ scores) and HBOT administration. Scores for the individual variables were marked as "delta" and represent the difference between the results at week five and baseline. Compared with controls, the HBOT group exhibited significant declines in MMP-9 concentration (127.91 vs -9.76; $p < 0.001$), RPQ-3 (-4.78 vs -2.82; $p < 0.001$) and RPQ-13 scores (-19.62 vs 12.78; $p < 0.001$).

Discussion

Based on their timing and different distinctive underlying pathomechanisms, head traumas are categorized as primary or secondary brain injury.²⁶ Secondary brain injury occurs in the weeks following, and in response to, the primary brain injury, which occurs at the time of and is directly caused by the trauma itself. Patients with secondary brain injury experience biochemical, metabolic, and cellular changes that are orchestrated by a complex biochemical cascade that causes increased intracranial pressure, BBB damage, neuroinflammation, brain edema, brain hypoxia, ischemia, and neurodegeneration.²⁷ The outcome of TBI is dependent on the secondary brain injury process.²⁸ The starting point of our study is based on this secondary pathomechanism and its reversible, dynamic nature.

The ECM and BBB both play important roles in neuroplasticity.²⁹ An imperative factor in the damage of the BBB is MMP-9, which is produced by microglia, the first line of defense against brain injury. As the sensors and effectors of the brain's immune system, microglial activity is the primary marker of neuroinflammation.^{30,31}

Table 2. Serum MMP-9 levels and RPQ scores in the HBOT and control groups.

Variable ^b	Total (N = 20)	Control (n = 10)	HBOT (n = 10)	p ^a
MMP-9 (ng/mL)				
Baseline	100.6 ± 17.4	113.1 ± 16.2	88.2 ± 5.9	< 0.001
Week 1	91 ± 17.9	105 ± 13	77.1 ± 8.8	< 0.001
Week 3	78.2 ± 21.1	96.6 ± 11.5	59.8 ± 7.4	< 0.001
Week 5	69.5 ± 24.2	91.3 ± 10.2	47.6 ± 8.3	< 0.001
Delta	-31.2 ± 13.5	-21.7 ± 8.5	-40.6 ± 10.7	< 0.001
RPQ Score				
Baseline				
RPQ-3	10.9 ± 0.9	10.7 ± 0.9	11.1 ± 0.9	0.340
RPQ-13	37.2 ± 3.1	36.8 ± 2.8	37.6 ± 3.4	0.574
Week 5				
RPQ-3	4.8 ± 1.9	6.5 ± 1	3.1 ± 0.3	< 0.001
RPQ-13	21.9 ± 8.1	29.6 ± 2.4	14.2 ± 1.2	< 0.001
Delta				
RPQ-3	-6.1 ± 2.2	-4.2 ± 1	-8.0 ± 1.1	< 0.001
RPQ-13	-15.3 ± 9	-7.2 ± 3.5	-23.4 ± 3.7	< 0.001

Note: Table 2 shows even distribution of RPQ scores from patients in the two study groups since baseline, thereby minimizing the possibility of selection bias that might be feared due to the allocation of treatment without randomization. Similarly, the mean reduction in serum levels in the HBOT group was significantly greater than controls (40.6 ng/mL vs 21.7 ng/mL; p < 0.001), therefore the suspicion that the serum MMP-9 values of patients with HBOT were lower than controls simply because they had been so from the start can be ruled out. Moreover, Table 2 also displays the analysis of relationship between variables which includes the interaction between the choice of therapy and the time of the examination.

Abbreviations: SD = standard deviation, HBOT = hyperbaric oxygen therapy.

^at-test for numeric variables, Fisher's exact test for categorical variables.

^bDelta is the difference between pre-treatment and week 5.

Figure 1. Changes in serum MMP-9 levels over time (Note: HBOT = hyperbaric oxygen therapy, 1 = pre-treatment, 2 = week 1, 3 = week 3, 4 = week 5).

Figure 2. Changes in MMP-9 levels in the HBOT and control groups.

Figure 3. MMP-9 concentration over time.

Enzymes such as occludin and claudin cause the basal degradation of endothelial lamina by targeting laminin, fibronectin, collagen, proteoglycan, and tight junction proteins (degradation of ZO-1), which are also the two main functional elements of the BBB.³² The downstream outcomes of the enzymatic digestion of these structural proteins include cytoskeletal damage, the disruption of cellular homeostasis, ischemia, inflammation, tissue necrosis, and apoptosis.³³

The stability of the microenvironment surrounding neurons, including the ECM, is necessary for healthy brain function. This stability is sustained by the BBB to maintain brain homeostasis and prevent cell death and dysfunction.³² The integrity of the BBB is the key to the restoration of brain homeostasis after physical injury. The BBB plays a pertinent role in this process because its integrity is influenced by MMP-9 activity, a major effector in secondary brain injury. Therefore, MMP-9 represents a reliable, relevant biological marker for predicting TBI outcome.³⁴


```

Linear mixed model fit by maximum likelihood ['lmerMod']

Random effects:
Groups   Name              Variance Std.Dev.
Medrec   (Intercept)      76.54    8.749
Residual                  25.02    5.002
Number of obs: 80, groups: Medrec, 20

Fixed effects:
              Estimate Std. Error t value
(Intercept)  113.084    3.187    35.485
Group        -24.872    4.507    -5.519
factor(time)2  -8.126    2.237    -3.633
factor(time)3 -16.527    2.237    -7.388
factor(time)4 -21.742    2.237    -9.719
group: factor(time)2 -2.966    3.164    -0.938
group: factor(time)3 -11.914    3.164    -3.766
group: factor(time)4 -18.832    3.164    -5.953

Analysis of Deviance Table (Type II Wald chisquare tests)

Response: MMP9
              Chi sq Df Pr(>Chi sq)
Group         66.967  1  2.761e-16 ***
factor(time)  454.441  3  < 2.2e-16 ***
group: factor(time)  44.216  3  1.358e-09 ***
---
Signif. codes:  0***0.001**0.01*0.05.      0.1 1

```

Figure 4. Linear mixed model output for MMP-9 serum levels, treatment group, time of examination, and their interaction as fixed effects.

Table 3. Regression model of the relationship between treatment type, MMP-9 serum level, and RPQ scores.

Outcome	HBOT vs Control	
	β (95% CI)	P-value
MMP-9	-18.83 (-27.91; -9.76)	< 0.001
RPQ-3	-3.80 (-4.78; -2.82)	< 0.001
RPQ-13	-16.20 (-19.62; -12.78)	< 0.001

Note: CI = confidence interval.

In the present study, HBOT was administered to prevent or inhibit MMP-9 production. HBOT acts on the neutrophil adhesion mechanism in endothelial cells. More specifically, HBOT reduces the expression of endothelial adhesion molecules and inhibits neutrophil adhesion molecule clustering, thus reducing the number of neutrophils adhered to endothelial cells. Decreasing the number of neutrophils activates pro-inflammatory processes including the release of pro-inflammatory cytokines (e.g., IL1B, IL-6, IL8, and TNFa) and decreases the expression of MMP-9.³⁵

The results of this study demonstrate HBOT's ability to inhibit the production of MMP-9. Similarly, a study in Canada found improved cognitive function, quality of life, and elevated brain activity in patients with mild TBI and prolonged post-concussion syndrome after 40 HBOT sessions over two months.³⁶

In another study, 40 rats were subjected to dynamic cortical deformation (DCD) and then divided into three treatment groups three hours after the initial trauma. 20 rats received HBOT with 100% oxygen at 2.8 ATA for 45 minutes, 10 received 100% oxygen for 45 minutes under normobaric conditions (1 ATA), and 10 were untreated (controls). Neuroinflammatory markers (TIMP-1 and TIMP-2) and MMP-9 levels were measured 96 hours after treatment. MMP-9

levels were found to be significantly lower in the HBOT group relative to controls. Inflammatory infiltration around the focus of necrotic brain tissue was prominent in most untreated animals and was composed predominantly of myeloperoxidase-positive neutrophils. Both normobaric and hyperbaric hyperoxia resulted in a significant decrease of neutrophil infiltration (GLM ANOVA main effect of treatment group: $P < 0.0001$; This reduction in the neuroinflammatory response was more extended with HBOT in comparison with normobaric hyperoxia (Tukey-Kramer $P < 0.05$).¹²

HBOT decreases intracranial pressure (ICP), reduces cerebrospinal fluid (CSF) pressure in patients with acute brain injury, restores the metabolic activity of the substance grisea in a single-photon emission computerized tomography scans of the closed head injury, and to restore glucose metabolism after brain injury.^{37,38} HBOT decreases mortality rates and improves the functional outcome of patients with severe head injuries. In such chronic brain injuries, HBOT increases cerebral blood flow, improves neuropsychological disorders, and promotes neurophysiological and electrophysiological recovery.³⁹

Several studies have reported that multiple HBOT sessions can improve neurological deficits and cognitive impairment in both acute and advanced chronic phases of head injury in rats.^{40–42} The long-term therapeutic effects of HBOT are derived from the induction of angiogenesis, neuroplasticity, and proliferation and differentiation of nerve stem cells. When HBOT was administered within three hours post-injury in a fluid percussion mouse model of TBI, there was a significant increase in the number of endothelial cells, neurons, and new glial cells four days after the initial injury.⁴⁰ Ten daily HBOT sessions at 2.5 ATA for 60 minutes enhances neuroplasticity by increasing axonal sprouting and synapse remodeling, contributing to the restoration of locomotor function in rats with TBI.⁴² Harch et al. study on the blood vessel density was measured bilaterally in the hippocampus using diaminobenzidine staining and correlated with MWT performance (Morris Water Task). They found increased vascular density in the bruised hippocampus and improved cognitive function in these rats after consecutive HBOT sessions (7 days/week, 1.5 ATA, 90-minute sessions/HBOT) over 40 days.⁴³ Several signaling pathways and transcription factors have been implicated in HBOT-induced neurogenesis including, wntless-related integration site, hypoxia-inducible factors, and cAMP response element-binding.⁴⁴

The outcome of this study was evaluated by the RPQ. RPQ-13 scores range from zero to 52, with higher scores reflecting more severe post-concussion syndrome. The RPQ-13 items encompass a group of advanced symptoms while the RPQ-3 symptoms include headaches, dizziness, and nausea. All those symptoms included in RPQ highly impact patient participation in social activities, psychosocial functioning, and lifestyle.¹⁷ During the three to six months typically required to resolve these symptoms patients are advised to gradually resume their routine activities. If symptoms do not resolve within this period, patients are usually often referred to a specialist for further assessment and treatment services.⁴⁵

The data collected in the present study showed a notable decrease in the RPQ-3 and RPQ-13 scores. There was no significant difference in the baseline RPQs of the groups at the beginning of the study. However, by the end of the five weeks of treatment, the patients receiving HBOT had much better RPQ scores (mean 3.1 vs 6.5 for RPQ-3, and 14.2 vs 29.6 for RPQ-13; both p -values < 0.001). As a result, the delta score from baseline to the end of week five in the HBOT group was significantly lower than the control group [-8.0 vs -4.2 for RPQ-3 ($p < 0.001$), -23.4 vs -7.2 for RPQ-13 ($p < 0.001$)].

The decline in RPQ scores over time was significant. RPQ-3 (-3.80 ($p < 0.001$)) and RPQ-13 (16.20 ($p < 0.001$)). HBOT administration in patients with mild TBI contributed to this improvement RPQ scores. Based on the findings described here, HBOT confers great benefits by improving the quality of life of patients with mild TBI and likely prevents further brain damage by increasing cerebral blood flow, improving neuropsychological disorders, and promoting neurophysiological and electrophysiological recovery. Given that repeated HBOT sessions restored neurological deficits and cognitive impairment, HBOT should be incorporated as a therapeutic modality for the treatment of patients with head injuries. Although there are many benefits of HBOT, there are also several drawbacks such as seizures, oxygen poisoning, pneumothorax, and middle ear injuries.

Although this study supports the efficacy of HBOT in treating post-concussion syndrome, the small sample population and single biomarker are limitations that must be addressed in future studies. The kinetics and underlying mechanisms of HBOT also warrant further investigation to maximize the many beneficial effects of HBOT.

Conclusions

HBOT effectively relieves the symptoms associated with post-concussion syndrome through a mechanism that involves repressing MMP-9 activity.

Consent statement

Written informed consent for publication of the patients' details was obtained from the patients/a guardian of the patient.

Data availability

Underlying data

Zenodo: Hyperbaric oxygen therapy ameliorates the symptoms of post-concussion syndrome by inhibiting MMP-9 activity: A Randomized Controlled Trial in Indonesia. <http://doi.org/10.5281/zenodo.4785703>.⁴⁶

This project contains the following underlying data.

- Maximilian Data Post-Concussion Syndrome 2.docx (Patient characteristics)
- Maximilian Data Post-Concussion Syndrome.xlsx (Human Matrix Metalloproteinase 9 (MMP-9) VALUE)

Reporting guidelines

This project also contains the following reporting guidelines.

- CONSORT checklist
- CONSORT flowchart

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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Shai Efrati

Nephrology Department, Assaf Harofeh Medical Center, Zerifin, Israel

The article entitled "Hyperbaric oxygen therapy ameliorates the symptoms of post-concussion syndrome by inhibiting MMP-9 activity: a randomized controlled trial in Indonesia" evaluated whether HBOT can accelerate the healing process, by measuring MMP, and reduces symptoms in patients with post-concussion syndrome by RPQ scores.

The study included 20 patients with post-concussion syndrome who were randomized into HBOT and control groups. HBOT reduced serum MMP-9 levels and improved the the RPQ scores.

The study suffers from major issues that needs to be address.

- What was the exact HBOT protocol? What does it mean 2-3 ATA? Was it 2 or 3? Based on what it was decided?
- Were only 3 sessions of HBOT given?
- If somebody refused to receive HBOT, it is problematic to have them as a control since it is selection bias. It is higher significant since the sample size was relatively small.
- The different in the baseline MMP mark the different between treatment and control groups.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hyperbaric oxygen therapy, brain, traumatic brain injuries

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 22 Oct 2021

Maximillian Christian Oley, Sam Ratulangi University, Manado, Indonesia

Although several studies have shown favorable outcomes from incorporating HBOT at 1.5-2.4 ATA in the management of post-concussion syndrome, there isn't an established protocol for the use of HBOT in this field.¹⁻³ It is difficult homogenize our subjects since the level of tolerance is different in each patient. Also, patients did not receive HBOT simultaneously, this was an accumulation of our patients treated in the surgery department over a period of 6 months.

Yes, 3 HBOT session were given.

Even though the control group had higher MMP-9 levels at baseline, this was compensated for by the highly significant endpoint difference (the difference between both scores (delta) after five weeks). Moreover, to increase the validity of our study, we used another method of evaluation, which was the RPQ scores.

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Competing Interests: No competing interests to disclose.

Reviewer Report 28 June 2021

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David X. Cifu

Department of Physical Medicine & Rehabilitation, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

This is a small (n=20), unblinded RCT of low dose HBOT (three 60 minute sessions at b/n 2-3 ATA over 5 weeks) in middle-aged (mean 39 years old) people with (what were labeled) as mild TBI. The researchers identified reductions in serum MMP-9 and symptoms (RPQ) after 6 weeks.

Unfortunately, this study is significantly underpowered, flawed in its diagnosis of mTBI (70% had intracranial bleeding, including SDH, EDH and IPH - the diagnosis of mTBI precludes these conditions), does not provide the specific time post-injury, the dosing of HBOT is atypical for mTBI trials, the controls refused to be in the HBOT arm (apparently that was by design?) and thus were negatively biased, and there was no HBOT sham so the treatment subjects were positively biased toward improvement.

Additionally, the authors have misquoted the mTBI/HBOT literature (e.g., references #14 and 15 do **not** support the efficacy of HBOT for mTBI) and do not seem to be aware of the HBOT literature. Of note, the abstract records the average age of participants as 60 years old, but the results section and tables identify it as 39 years old.

This study has too significant methodological limitations and inconsistencies to warrant indexing.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TBI, HBOT, mild TBI, Rehabilitation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 12 Jul 2021

Maximillian Christian Oley, Sam Ratulangi University, Manado, Indonesia

The severity of TBI is assessed according to the GCS grading of the level of consciousness. Mild TBI can also be associated with intracranial lesions such as ICH, EDH, SDH, depressed fractures, etc. The space in the subarachnoid, interhemispheric, and cistern create room for compensation, thus mitigating the severity of the injury. Therefore, regardless of the size of the lesion, there is still tolerance so that symptoms will not be as severe. This is in accordance with the Monroe-Kelly law.

This study was conducted on actual patients, not on animals, therefore it is difficult to reach homogeneity on our test subjects. We were unable to control the exact post-injury time as the time of injury and hospital transfer varies between patients, however, most patients received HBOT approximately one-week post-injury.

In addition, to our knowledge, there is no guideline for HBOT dosing in brain injuries. The optimal oxygen dose and duration vary among several studies which makes the comparison process complicated and biased interpretations.

Lastly, apologies for the difference in the results on the abstract from the results section. The average age of patients was 39 years.

Competing Interests: None

Comments on this article

Version 1

Reader Comment 17 Dec 2021

Julius July, Dept of Neurosurgery, Medical Faculty, Universitas Pelita Harapan, Jl. Siloam No 6, lippo Village, Tangerang, Banten, Indonesia

It's an interesting study to see the impact of HBOT. Several concern regarding the result are:

1. The predominant age group in this study (around 60), also I would like to see the mechanism of injury.
2. Laboratory result often not associated with clinical features of patients. I would like to see the clinical characteristic of the patient before and after HBOT, such as GCS, neurological function, etc. The clinical part will strengthen this study and should be addressed in the discussion.
3. The conclusion in this study probably better with minor revision. There are so many pathway that could be associated with this HBOT treatment for concussion, and one of them is associated with MMP family. We should not certainly say "thorough" one pathway in this study.

Overall, I still consider this is an interesting study for traumatic brain injury.

Competing Interests: None

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