RESEARCH ARTICLE

Effect of mild hyperbaric oxygen therapy on children diagnosed with autism

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ABSTRACT

Introduction: Hyperbaric oxygen (HBO_2) therapy is emerging internationally as the primary treatment modality for inflammatory pathways related to neurological disorders. Currently, literature concerning its effectiveness in autistic children is limited. Using neurocognitive tests and clinical-diagnostic evaluations, this study evaluates the clinical, cognitive and behavioral effects of HBO_2 on children diagnosed with autism.

Methods: An experimental HBO_2 group (EXP: F = 1; M = 7; mean age: 7 ± 2.33; years) and a control non-HBO_2 group of autistic children (CTRL: F = 2; M= 5; mean age: 6.6 ± 2.7 years) correctly completed the Aberrant Behavior Checklist-Community (ABC) before HBO_2 (T_0), after 40 sessions of HBO_2 (T_1), and one month after the end of treatments (T_2). Additionally, the experimental HBO_2 group was evaluated with the Childhood Autism Rating Scale at T_0 and T_2.

Results: Total ABC score was lower at T_2 (mean ± SD: 50.38 ± 18.55; $p < 0.001$) compared to scores obtained at T_0 (mean ± SD: 57.5 ± 19.01). Similarly, in the control group the total ABC score differed statistically ($p < 0.05$) between T_0 (103.6 ± 20.38) and (T_2: 59 ± 25.25).

Conclusions: Despite the improvements reported in both groups, our results do not support the utility of HBO_2 in children diagnosed with autism.

KEYWORDS: autism; children; hyperbaric oxygen therapy; psychology

INTRODUCTION

Autism (AD) is a neurodevelopmental disorder characterized by impaired social interaction and communication that presents with narrow and stereotyped patterns of behaviors. Although the estimated rate of AD in the United States is one per 100 people [1], previous epidemiologic studies have implied that the prevalence of the pathology is increasing [2,3]. Annual treatment costs of AD within the United States exceed several billion dollars [4]. With autism rates increasing and costs on the rise, better and cheaper treatments are continually being developed.

Hyperbaric oxygen (HBO_2) therapy is an emerging treatment modality for inflammatory pathways related to AD [15,16]. According to the Undersea and Hyperbaric Medical Society (UHMS), HBO_2 is defined as an intervention that utilizes 100% patient-inspired oxygen inside a chamber pressurized to greater than 1.4 atmospheres absolute (ATA). These environmental conditions increase the partial pressure of oxygen (PPO_2) and dissolved oxygen in plasma, increasing the oxygenation of body tissues [17].

To date the UHMS has determined the beneficial effect of HBO_2 for 14 different diseases [18]. An increasing number of studies are reporting that HBO_2 improves neurological function. In particular, Jacobs, et al. demonstrated significant and persistent gains of cognitive function and memory in a group of people with cognitive deficit receiving HBO_2 at 100% and 2.5 ATA after 30 intermittent sessions [19]. Additionally, a double-blind randomized controlled trial showed that even young healthy adults treated for seven weeks

with oxygen improved their cognitive performances, attention, and both immediate and delayed word recall when compared to a group breathing air [20]. This study investigates the efficacy of low-pressure HBO_2 at 1.5 ATA for autistic children breathing 100% oxygen. The aim of the study was to evaluate clinical, cognitive and behavioral changes through neurocognitive tests and clinical diagnostic evaluation before and after HBO_2 therapy.

METHODS

This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki. All participants' parents gave their informed consent, and every precaution was taken to protect their privacy. All costs of treatment and testing were covered by Domus Medica, ASPATI and private donations.

Patient selection

All children prescreened for this study were diagnosed with AD by an independent pediatrician and were referred by their primary care physician for the experimental treatment. AD diagnoses were based on DSM IV diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) and confirmed by a separate pediatric neuropsychiatrist prior to study enrollment; children with other pervasive developmental disorders and/or Asperger syndrome were excluded from this study. Patient screening to determine eligibility for HBO_2 included an electrocardiogram, chest X-ray, and full examination by an otorhinolaryngologist to check the integrity of the tympanic membranes of each ear; patients with active infections and/or a previous surgery were excluded from the study.

A total of 40 autistic children were prescreened for study eligibility. A total of 28 patients were removed from the study, 16 of whom failed to meet the study inclusion criteria, 10 of whom were deemed too noncompliant for HBO_2, and two of whom had parental consent withdrawn prior to treatment. The remaining 12 subjects received 40-hour long sessions of HBO_2. During the active portion of the study, four subjects were unable to complete the clinical, cognitive and behavioral tests. The final experimental cohort consisted of eight children, (EXP: F = 1; M = 7; mean age: 7 ± 2.33; years). Of the 10 patients deemed too noncompliant to receive HBO_2, seven agreed to continue on to the active phase of the study as part of a control group (CTRL: F = 2; M = 5; mean age: 6.6 ± 2.7 years). Members of the control group did not receive hyperbaric oxygen therapy. All patients involved in this study were kept on a strict diet and restricted from beginning any new therapy for the duration of the study.

Nutritional considerations

Nutrition was standardized for all study subjects with the intent of minimizing proinflammatory sources of nutrition. All patients followed the same nutritional regimen suggested by their own pediatrician before beginning the study; no subjects changed their nutritional habits before or during the study. As gluten has been demonstrated to stimulate inflammatory processes at a local level and to have direct involvement in intestinal permeability[21], foods that contained gluten were eliminated from the diet when possible or replaced with gluten-free products where the gluten was substituted by a different protein. In particular, bread and its derivatives as well as pasta made with wheat flour were excluded.

Meat-based foods, both white and red meat and including cold cuts, were minimized. The objective of this choice was the reduction of proinflammatory factors – in particular insulinlike growth factor 1 (IGF-1) and interleukin 1 (IL-1), which are related to meat consumption [21]. A pediatric nutritionist was consulted to ensure all subjects would maintain proper nutrition in terms of calories, vitamins and minerals for the duration of the study.

HBO_2 protocol

Patients were exposed to HBO_2 inside a multiplace hyperbaric chamber with compressed air at 1.5 ATA for 80 minutes. Each patient was provided with a well-sealed breathing mask that provided 100% oxygen. Oxygen concentration in the mask was measured every five minutes by sampling outside the chamber in order to ensure adequacy of the gas supply and the ability of providing a tight seal around the face. Children were accompanied by a parent and health care assistant to ensure patient health, safety and treatment compliance for the duration of the HBO_2 sessions. Subjects, parents, and assistants present in the hyperbaric chamber were additionally monitored by staff outside the chamber. Each patient received eight weeks of HBO_2 treatments once a day, from Monday to Friday for a total 40 HBO_2 sessions.

Table 1. Scores from aberrant behavior checklist-community

EXP (n=8)	ABC T_0	ABC T_1	ABC T_2
mean	57.50	55.25##	50.38***
SD	19.01	18.96	18.55
CTRL (n=7)	**ABC T_0**	**ABC T_1**	**ABC T_2**
mean	103.6	94.86	59.00§
SD	20.38	17.22	25.25

For both control and experimental HBO_2 groups, the mean values ± SD obtained before (T_0), at the end of 40 sessions of HBO_2 (T_1), and one month after the end of HBO_2 (T_2) are shown. Statistics of their differences is also reported. ## ABC T_1 vs ABC T_2 ($p < 0.01$); ***ABC T_0 vs ABC T_2 ($p < 0.001$); § ABC T_0 vs ABC T_2 ($p < 0.05$)

Clinical and behavioral assessments

Each patient underwent the Aberrant Behavior Checklist-Community (ABC is an evaluation based on observations. ABC consists of a 58-item questionnaire that measures communication, social interaction, play and stereotyped behaviors. It is regularly used to evaluate the efficacy of therapeutic interventions; scores range from 0 ("not a problem at all") to 3 ("severe degree of problem"). The final outcome is calculated by adding the scores from five distinct categories assessing:

- sensory responses (ABC-1);
- affective responses (ABC-2);
- stereotypies and use of objects (ABC-3);
- language development (ABC-4); and
- individual and social autonomies (ABC-5).

The ABC questionnaire was applied three times to both the experimental HBO_2 and control groups: before starting the study (T_0), at the end of 40 sessions of HBO_2 (T_1, at 60 days) and one month after the end of HBO_2 sessions (T_2, at 90 days). The cutoff points for diagnosis of AD were identified as:

- high probability of autism (> 67 points);
- uncertain (53-65 points);
- low probability of autism (< 53 points).

Lower scores indicate less severe autism.

The Childhood Autism Rating Scale (CARS) was utilized in the experimental group. CARS is one of the most widely standardized and common test to diagnose AD and asses its severity [22]. It can be applied to children older than 2 years old and consists of 15 different items that describe in detail the crucial features of diagnosis. A score with a range between 1 to 4 shows the severity of the symptoms (1 = none, 4 = severe expression). Total score was the sum of all the scores obtained from each item; a score of 30 represents the lowest value to diagnose autism. These values were obtained only in the eight study subjects before HBO_2 (T_0) and at the 90-day visit (T_2).

Data analysis

All data were expressed as mean ± standard deviation (SD) and compared with the statistical GraphPad Prism software (GraphPad Prism 6, GraphPad Software Inc., San Diego, California). After a normality test (D'Agostino-Pearson omnibus normality test), ABC scores in T_0, T_1 and T_2 were analyzed with a parametric test for multiple comparisons (one-way analysis of variance/ANOVA). The Student's t-test was used to compare scores from the CARS scale in T_0 and T_2. $P < 0.05$ was considered significant.

RESULTS

ABC

Mean scores and standard deviations are summarized in Table 1. The ABC questionnaire was also administered before treatment (T_0), after 40 HBO2 sessions (T_1) and one month after the end of treatments (T_2). Total ABC score, including all five categories, was lower in T_1 (mean ± SD: 55.25 ± 18.96; ns) and T_2 (mean ± SD: 50.38 ± 18.55; $p < 0.001$) compared to scores obtained in T_0 (mean ± SD: 57.5 ± 19.01). Additionally, a significant difference was found in comparing scores between T_2 and T_1 ($p < 0.01$). In particular, sensory responses (ABC-1) and language development (ABC-4) were categories benefiting the most from HBO_2 treatment. The ABC-1 score in T_2 (mean ± SD: 4,87 ± 3,13; $p < 0.05$) was lower than T_0 (mean ± SD: 6,125 ± 3,18). ABC-4 score in T_2 (mean ± SD: 11.25 ± 3.65; $p < 0.001$) and T_1 (mean ± SD: 13.63 ± 3.62; $p<0,05$) were lower than T_0 (mean ± SD: 14.75 ± 3.69).

Scores obtained from ABC-2 (affective responses), ABC-3 (stereotypes and use of objects) and ABC-5 (individual and social autonomies) did not modify during therapy. The result suggests that HBO_2 may improve sensorial responses, language development and use in autistic children, as lower scores indicate less severe ABC autism. Comparisons among different time-points within the control group (T_0: 103.6 ± 20.38; T_1: 94.86 ± 17.22; T_2: 59 ± 25.25) showed improvement of the total ABC score, statistically significant between T_0 and T_2 ($p < 0.05$). In detail, sensory responses (ABC-1; T_0: 14.57 ± 3.645; T_1: 12.29

± 1.49 and T_2: 7.85 ± 2.11) evidenced a significant difference between T_0 and T_2 ($p < 0.001$). Scores obtained as per affective responses (ABC-2; T_0: 28.71 ± 7.04; T_1: 27.14 ± 5.69 and T_2: 19.29 ± 5.52), language development (ABC-4; T_0 23.57 ± 7.61; T_1: 22.14 ± 7.40 and T_2: 11.86 ± 9.19) and individual and social autonomies (ABC-5; T_0: 19.43 ± 6.37; T_1: 17.71 ± 5.18 and T_2: 10.86 ± 7.08) showed no significant differences between the different time-points. Moreover, as per stereotypies and use of objects (ABC-3; T_0: 17.29 ± 2.360; T_1: 15.57 ± 1.39 and T_2: 9.143 ± 3.671) a significant improvement of scores was observed between T_0 and T_2 ($p < 0.001$).

CARS

The CARS test, used to help in diagnosing AD and assess its severity, was administered only to the experimental HBO_2 group as an additional test. It was performed before the therapy (T_0) and one month after the end of HBO_2 treatment (T_2). Obtained scores in T_2 (mean ± SD: 35.43 ± 3.29) did not significantly differ from those obtained in T_0 (mean ± SD: 36.31 ± 3.18), as shown in Table 2.

Table 2. Scores from childhood autism rating scale in the eight study subjects

	CARS	
SUBJECTS	**T_0**	**T_2**
1	34	34.5
2	38	38
3	33	32
4	35.5	32
5	37.5	36.5
6	38	38
7	32.5	32
8	42	40.5
mean ± SD	36.31 ± 3.18	35.43 ± 3.29
p-value	NS	

The mean values ± SD obtained before (T_0) and one month after the end of HBO_2 (T_2) are shown. Statistics of their differences (ns) is also reported.

DISCUSSION

Current literature on this subject is severely lacking. Case studies and related publications about effects of hyperbaric oxygenation on core and/or non-core symptoms of AD are insufficient, as most of them encountered multiple internal and external validity problems. This study aimed to investigate the therapeutic efficacy of HBO_2 for ameliorating cognitive and behavioral functions in children diagnosed with autism. Few studies have supported hyperbaric oxygen as a therapy able to improve neurological activity in patients with neurological disorders. However, HBO_2 has shown a positive effect in pathologies such as traumatic and chronic cerebral injury [23,24] and fetal alcohol syndrome [25,26]. Interestingly, the hyperbaric pressure (1.5 ATA or lower) used in the aforementioned studies [23-26] was lower than the pressure usually applied in daily clinical practice [27]. Moreover, HBO_2 at the same pressure has shown improvement in patients with cerebral palsy (CP) [28], with considerable effect on the results in some cases [29]. Improvements have also been demonstrated in a traumatic brain injury model in rats. Harch and colleagues demonstrated an improvement of memory and spatial learning in brain-damaged rats treated with HBO_2 (100% O_2 at 1.5 ATA) compared with rats exposed to a normobaric environment [30].

An important point of discussion is the hypothesis that high oxidative stress levels exist in autistic individuals [31], which could be due to an impaired antioxidant potential [32,33]. The relationship between HBO_2 and oxidative stress remains controversial. Indeed, studies have shown that HBO_2 may respectively cause an increase [34] or decrease [35] in oxidative stress at pressures under 2 ATA. Prolonged and repeated use of low-pressure HBO_2 may decrease lipid peroxidation [36] as well as activity of the antioxidant enzymes such as superoxide dismutase (SOD) [37,38], glutathione peroxidase [39], catalase [40] and paraoxonase enzyme [36]. Regardless, no worsening of autistic subjects' oxidative profile post-HBO_2 has been encountered within the literature [15-17].

In recent studies, those autistic subjects who received a low hyperbaric pressure (1.3 to 1.5 ATA) with variable oxygen concentration (between 21% and 100%) showed a significant improvement in both their clinical responses and inflammatory status [13,15,17]. Although some doubts concerning oxidative stress in association with HBO_2 were raised [41], HBO_2 is considered safe for children, even at 2 ATA for two hours a day [42]. However, the lack of clear evidence between 1.3 and 1.5 ATA with air or oxygen treatments requires caution.

LIMITATIONS

Our study showed short-term improvements in both groups, but it has several limitations. A randomized blinded protocol with a larger and more homogenous clinical sample is needed to strengthen our results. The basal ABC scores of the control group were nearly double that of the experimental group. Further, the ABC metric in of itself is flawed due to its dependence on an outside observer such as a parent or caregiver. The CARS test is by far a more objective measurement of the subjects' cognitive function and severity of their disorder. However, this test was utilized only in the experimental group.

Though a specific food model was designed and prescribed to the children, dietary compliance is often difficult to maintain especially in this specific subpopulation of patients. Additional research is needed to clarify a nutritional approach for autistic children.

CONCLUSIONS

HBO_2 appears to be safe for autistic children. The probable improvement in certain autistic behaviors need to be further elucidated. HBO_2 seemed to improve neurocognitive evaluation in the experimental HBO_2 group after 40 treatments, with stabilized improvement up to 90 days. Similarly, the control group underlined a significant difference before treatment and at follow up, but not at the 60-day visit. This study was well executed to prevent any risk, and the O_2 levels were well monitored at all times. The nutrition details were suggested, but food could not be controlled objectively. This study showed that with an anti-inflammatory diet HBO_2 seems to improve sense perception, relationships and personal capacity. Currently, the sustainability of this improvement is limited to 90 days, as no other measurements were taken past T_2. Considering the several limits of the present study and the improvement in both groups, our results do not support the utility of mild HBO_2 administration in children diagnosed with autism.

■

Conflict of interest statement

The authors declare that no conflict of interest exists with this submission.

Acknowledgments

We wish to thank Domus Medica Casa di Cura privata (San Marino Republic) for approving the experimental study and for covering the costs for the treatment.
In addition, we are thankful to Associazione Pazienti Trattati in Iperbarismo (ASPATI) for providing financial support, evaluating test, and researcher reimbursement.

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✦

RESEARCH ARTICLE

The relationship between intoxication severity and blood interleukin 6, interleukin 10 and CRP levels in carbon monoxide-poisoned patients

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ABSTRACT

Carbon monoxide (CO) is one of the most common causes of death due to intoxications. No biochemical marker is available to evaluate the severity of CO intoxication.

We measured high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and interleukin-10 (IL-10) levels in patients with different degrees of CO poisoning.

We prospectively included 40 CO-poisoned patients admitted to emergency services. Blood samples were collected from the patients at admission (0 hour) and after treatment (six hours). While all patients received normobaric oxygen (NBO_2) therapy, patients with severe CO poisoning received additional sessions of hyperbaric oxygen (HBO_2) therapy. Blood samples were also collected from a group of healthy volunteers (n=40). Serum IL-6 and IL-10 levels were measured with the ELISA method while hs-CRP was quantified by turbidimetric analysis.

At admission, IL-6 levels were significantly higher in the patient group compared to the control group (P=0.001), but IL-10 and hs-CRP levels were not significantly different between the groups. Compared to admission levels, IL-6 levels were higher at six hours (P=0.014). The patients were grouped according to treatment type (NBO_2, HBO_2) and history of syncope, but no significant differences were detected in patient subgroups regarding IL-6, IL-10 and hs-CRP levels. A weak positive correlation was found between COHb and lactate levels in patients (P=0.013; r=0.390).

This study shows that IL-6 level increases in CO-poisoned patients, but it is not correlated with the severity of the intoxication.

KEYWORDS: biomarkers; carbon monoxide; hs-CRP; hyperbaric oxygen therapy; interleukin 10; interleukin 6

INTRODUCTION

Carbon monoxide (CO) poisoning is one of the most common causes of intoxication-related deaths both in our country of Turkey and around the world [1,2]. CO poisoning incidence rises particularly in winter due to the use of heating sources without proper ventilation. The non-specific symptoms can easily mislead a diagnosis to other diseases. Hypoxia caused by poisoning affects many oxygen-consuming tissues and organs, particularly the heart and the brain.

CO poisoning affects the body in several ways. As CO affinity to hemoglobin is 240 times greater than that of oxygen, it binds to hemoglobin and hemoproteins such as cytochrome c oxidase and myoglobin, causing tissue and cellular hypoxia respectively. CO precipitates platelet-neutrophil aggregation, xanthine oxidase formation on vascular endothelium and lipid peroxidation. Moreover, it leads to neuronal apoptosis by increasing glutamate and N-methyl-D-aspartate (NMDA) receptor activation in the brain. All of these pathophysiological mechanisms are shown to be related to inflammation [3,4].

CO poisoning is treated with oxygen, either normobaric (NBO_2) or hyperbaric oxygen (HBO_2). NBO_2 treatment is the use of 100% oxygen at normal atmospheric pressure, whereas HBO_2 is defined as 100% oxygen breathing at pressures higher than sea level pressure (1 atmosphere absolute/ATA). Although the most recent version of Hyperbaric Oxygen Therapy Indications, 13th edition, of the UHMS recommends HBO_2 therapy for all patients with CO poisoning regardless of severity, HBO_2 therapy is typically reserved for patients with severe poisoning [5-7].