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Randomized trial of hyperbaric oxygen therapy for children with autism

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ABSTRACT

Autism Spectrum Disorders (ASDs) are characterized by the presence of impaired development in social interaction and communication and the presence of a restricted repertoire of activity and interests. While numerous treatments for ASDs have been proposed, very few have been subjected to rigorous scientific investigation. Hyperbaric oxygen therapy (HBOT) has been recently popularized as a treatment for the symptoms of ASDs. The purpose of this study was to test the hypothesis that HBOT would have a beneficial effect on ASD symptoms in the context of a double-blind placebo-controlled trial. This randomized double-blind placebo-controlled trial compared HBOT used to deliver 24% oxygen at 1.3 atmospheric pressure ($n = 18$) to placebo ($n = 16$) in children with Autistic Disorder. Both direct observational measures of behaviors symptomatic of autism and standardized psychological assessments were used to evaluate the effects of the treatment. No differences were detected between HBOT and placebo groups across any of the outcome measures. The present study demonstrates that HBOT delivered at 24% oxygen at 1.3 atmospheric pressure does not result in a clinically significant improvement of the symptoms of Autistic Disorder.

Autism Spectrum Disorders (ASDs) are characterized by the presence of impaired development in social interaction and communication and the presence of a restricted repertoire of activity and interests (APA, 2000). The etiology of ASD is not currently known, which may in part explain why numerous widely divergent treatments for ASDs are in regular use (Green et al., 2006). Very few interventions for ASDs have been subjected to controlled scientific research. Notable exceptions include Applied Behavior Analysis (ABA; Myers & Plauché Johnson, 2007; Rogers & Vismara, 2008), risperidone (McDougle et al., 2005), and treatments demonstrated to be ineffective, such as secretin (Williams, Wray, & Wheeler, 2005), and facilitated communication (Jacobson, Mulick & Schwartz, 1995).

Hyperbaric oxygen therapy (HBOT) is a commonly used treatment for ASDs that has been increasing in prevalence in recent years. HBOT involves delivery of a mixture of gases ranging from room air (21% oxygen) to 100% oxygen at atmospheric pressures above ambient pressure (atm). Each treatment session consists of a compression cycle during which the pressure is increased slowly to allow for equilibration of air pressure in the ears and sinuses, followed by a period where air is delivered at the target pressure, usually for approximately 60 min. The dose of HBOT is a function of the pressure, the concentration of oxygen, the duration of exposure, and the frequency and total number of treatment sessions (Leach, Rees, & Wilmhurst, 1998).

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HBOT is a scientifically supported treatment for decompression sickness (Leach et al., 1998) and is still under investigation for wound healing (Rodriguez, Felix, Woodley, & Shim, 2008). Early uncontrolled reports of HBOT for the treatment of neurological disorders, such as cerebral palsy (CP), described dramatic effects. A subsequent randomized placebo-controlled trial of 1.3 atm air to 1.75 atm 100% oxygen, however, failed to corroborate anecdotal reports (Collet et al., 2001). Similar to early reports of HBOT for the treatment of CP, there is anecdotal evidence suggesting that HBOT may be an effective treatment for ASDs. The rationale for using HBOT for treatment of ASDs is based on the recent findings of oxidative stress (James et al., 2004) and neuroinflammation (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005) in ASDs and initial evidence that HBOT may alleviate oxidative stress in rats with pancreatitis (Yasar et al., 2003) and decrease inflammatory responses in rats (Lin, Wan, Wu, Tung, & Wu, 2005; Sumen, Cimsit, & Eroglu, 2001). Despite the fact that these findings are tentative at best, HBOT has become a popular treatment for ASD.

Rossignol & Rossignol (2006) published the first treatment study of HBOT use in ASD using a retrospective, uncontrolled, within-group design. Six participants were exposed to 40 compression cycles at 1.3 atm and 28–30% oxygen. Changes in scores on the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) were statistically significant. In a subsequent open-label prospective study by the same group, a group of children who received 24% oxygen at 1.3 atm were compared to a group who received 100% oxygen at 1.5 atm (Rossignol, Rossignol, James, Melnyk, & Mumper 2007). No difference between groups was observed. When data from both were combined, significant effects were found on the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) and the Autism Treatment Evaluation Checklist (ATEC; Autism Research Institute, 2008), an unvalidated measure.

In the first controlled study of HBOT for individuals with ASDs, Lerman et al. (2008) employed a multiple baseline design to evaluate changes on repeated direct measures of behavior across three children. Treatment consisted of 88% oxygen at 1.3 atm (via oxygen mask). Three classes of behavior were measured: (1) engagement in tasks, (2) spontaneous communication, and (3) problem behavior. No consistent response to treatment was observed.

Recently Rossignol et al. (2009) published a double-blind placebo-controlled trial of HBOT. The study compared a group that received 40 sessions of 24% oxygen at 1.3 atm to a group that received regular room air at 1.03 atm (control group). In an unusual statistical methodology, only within-group changes were contrasted and the authors found a greater degree of what they described as significant improvement within the treatment group. However, when data are analyzed for differences between the treatment and placebo groups, very few are found. Specifically, the difference between groups on the Aberrant Behavior Checklist (ABC; Aman & Singh, 1994), for total scores and subscales, are not statistically significant. The authors point out that the change from pre- to post-scores for the treatment group on the ABC total score was significant, and the control group was not, however the mean change within the treatment group was 8.8 points whereas the control group changed by 7.8 points, with standard deviations ranging from 17.3 to 28.7 points on these measures. A difference of one point between groups appears unlikely to be clinically significant. Analyses of the other described significant effects reveal similar findings. In particular, when the level of significance is corrected for alpha inflation, none of the numerous contrasts appear significant. Essentially, both groups improved as a function of participating in the study but the difference between groups was not significant, thereby seriously calling into question whether HBOT produced a meaningful treatment effect.

Existing research on HBOT leaves several points in need of further investigation. First, the only previous study to include a placebo group suffered from significantly flawed data analysis (Rossignol et al., 2009). Second, a broader range of dependent variables may need to be included when evaluating a novel treatment, in order to avoid failing to detect any possible effects. Third, all previous studies have included 40 or fewer treatment sessions and it is possible that more sessions would increase effectiveness. The purpose of this study was to evaluate the most commonly prescribed dose of HBOT for ASD (24% oxygen at 1.3 atm) over a relatively long duration (80 sessions), in a randomized placebo-controlled design.

1. Method

1.1. Experimental design

A randomized, double-blind, placebo-controlled design was used. Because ABA is a treatment of established effectiveness (Matson & Smith, 2008; Myers & Plauché Johnson, 2007), prior to group assignment, participants were matched in pairs on the number of hours of ABA treatment that they were receiving at the start of the study. Pairs of participants were also matched according to chronological age. A coin toss was then used to randomly determine which participant in each pair was allocated to which group. Matching and random assignment was done by an investigator who was blind to all participant details aside from participant number, age, and number of ABA treatment hours being received. The use of supplements, dietary modifications, and medical interventions were held constant for the duration of the study.

1.2. HBOT and placebo

Both groups received 80, 1-h sessions in the HBOT chamber with the only difference being the compression to 1.3 atm with supplemental oxygen (approximately 24–28% FiO_2) in the HBOT group and free airflow through the chamber at ambient pressure in the placebo group. The number of sessions per week was allowed to range from 6 to 10, however all participants were required to complete 80 sessions within 15 weeks or less. Participants' caregivers and all investigators involved in the study were kept blind to participant group assignment.

1.3. Apparatus

The Vitaeris 320 inflatable chamber (OxyHealth, Inc.) was selected for the study. It is supplied with external air through a 20 l/min compressor and was supplemented by a 10 l/min oxygen concentrator for the HBOT group.

1.4. Participants

Participants were recruited for this study from a large community-based provider of behavioral intervention services to children with ASDs. Recruitment occurred from August 2007, through December 2007. Inclusion criteria were as follows: (1) diagnosis of Autistic Disorder according to DSM-IV criteria and confirmed by the Autism Diagnostic Observation Schedule—Generic (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), (2) 2–14 years of age, (3) the primary language spoken in the home was English, (4) absence of any medical condition which might contraindicate HBOT (i.e., seizures, chronic or current sinus infections, or current otitis media), and (5) caregiver agreement to not introduce or alter any treatments during the study.

Forty six participants began the study and 12 withdrew, resulting in 18 HBOT participants and 16 placebo participants completing all 80 sessions and follow-up measures. The primary reason reported for withdrawal was the travel required to the clinic. One participant in the placebo group withdrew after having a seizure for the first time. Mean participant age was 6.18 (HBOT 6.11; placebo 6.25) and mean number of ABA treatment hours per month was 109 (HBOT 114.7; placebo 103.3).

All procedures were approved by the Institutional Review Board (IRB00004971) at the Center for Autism and Related Disorders. The study was registered at clinicaltrials.gov (NCT00404846). Informed consent was obtained for all participants in the study by an investigator meeting with participants' caregivers. Participants were required to visit their primary care physician prior to the first HBOT session to obtain written confirmation that they did not have any excluded medical conditions (listed above).

1.5. Psychological assessments

All assessments were conducted by trained assessors who were blind to group assignment. To maximize the study's ability to detect change in any symptom area relevant to autism, a large variety of assessments were used, including the following: the ABC (Aman & Singh, 1994), ADOS (Lord et al., 1999), Behavior Rating Inventory of Executive Functioning (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000), Clinical Global Impression Scale (CGI; Guy, 1976), Parent Stress Index (PSI; Abidin, 1995), Peabody Picture Vocabulary Test (PPVT-III; Dunn & Dunn, 1997), Repetitive Behavior Scale (RBS; Bodfish, Symons, & Lewis, 1999), SRS, Vineland Adaptive Behavior Scales—Second Edition (VABS-II; Sparrow, Cicchetti, & Balla, 2005), and the Beery-Buktenica Developmental Test of Visual-Motor Integration—5th edition (VMI-5; Berry & Berry, 2004). The ADOS, BRIEF, PPVT-III, SRS, VABS, and VMI-5 were administered pre and post-treatment. The ABC, CGI, and RBS were administered weekly. The PSI was administered four times, once at baseline, twice during treatment, and once at completion.

1.6. Direct observation procedures

Direct observations of behavior occurred twice weekly, throughout the study (Zarcone, Napolitano, & Valdovinos, 2008). Observations consisted of the "Toy Play" condition of the standard functional analysis (Iwata, Dorsey, Slifer, Bauman, & Richman, 1994). Partial interval data were collected on toy play, hyperactivity, appropriate vocalizations, vocal stereotypy, physical stereotypy, and challenging behaviors (i.e., aggression, self-injury, property destruction). Data were collected by trained observers who were blind to group assignment. Interobserver agreement (IOA) was collected for a minimum of 30% of observations with each participant (range 30.4–45.5%). Mean agreement for each participant was above 80% with a range of 81.8–100%.

1.7. Role of the funding source

External sources who contributed funding for this study had no role in the study design, collection of data, analysis and interpretation of data, writing of the manuscript, nor in the decision to submit the manuscript for publication.

2. Results

All statistical analyses described below were intent-to-treat analyses, which included all data which were available. No data were excluded from any analysis. In cases where data were not available for analysis, it was due to age restrictions on particular assessments or due to participants not availing themselves for assessment.

2.1. Primary outcome measures

The primary outcome measures were those that are symptomatic of autism: social reciprocity, communicative approach, and repetitive behaviors. Global changes in diagnostic classification were assessed via change in ADOS classification (data available for 18/18 HBOT and 16/16 placebo participants) and symptomatic changes at a more detailed level were assessed

Table 1
Group comparison on change scores for SRS subscales.

	Mean	S.D.	*t*	*p*-value	*d*
SRS social awareness change			−0.31	0.76	0.12
HBOT	−3.14	14.21			
Placebo	−1.33	16.62			
SRS social cognition change			1.47	0.15	0.55
HBOT	1.79	8.82			
Placebo	−5.33	16.01			
SRS social communication change			0.46	0.65	0.33
HBOT	−1.00	13.06			
Placebo	3.13	12.02			
SRS social motivation change			0.18	0.86	0.06
HBOT	−5.50	12.45			
Placebo	−6.33	13.12			
SRS autistic mannerisms change			0.99	0.33	0.37
HBOT	1.64	14.58			
Placebo	−3.33	12.49			

Table 2
Number of participants showing improvement on the ADOS.

ADOS subscale	Number of participants showing improvement		Fisher's exact test
	HBOT ($n = 18$)	Placebo ($n = 16$)	
Communication	3	2	1.0
Socialization	3	2	1.0
Total Score	5	4	1.0

via changes in SRS subscales (data available for 14/18 HBOT and 15/16 placebo participants). Change scores for the SRS were calculated by subtracting the participant's pretest score from their posttest score. There were no significant differences on the SRS change scores between groups (Table 1).

On the post-treatment ADOS classifications, 9 participants from both groups improved from a classification of Autistic Disorder to Autism Spectrum. None of the participants improved into the non-ASD category. To analyze for group differences in improvement on ADOS cut-off scores, Fisher's exact test was conducted. No significant differences were observed between groups (Table 2).

2.2. Secondary outcome measures

The VABS-II, VMI-5, PPVT, and BRIEF (number of participants for whom data were available is depicted in Table 4) were analyzed as secondary outcome measures. At baseline, there were significant differences for BRIEF-P Emotional Control (Wilcoxon $p = 0.023$) and BRIEF-P Behavior Regulation Index (Wilcoxon $p = 0.046$), with higher sample means for the placebo group. There were no significant differences among groups for any of the other assessment subscales.

Subscale change scores on the secondary outcome measures were created by subtracting baseline scores from the post-treatment scores. There were no significant differences in change scores for any of the secondary outcome measures (Table 3).

Direct observation data were available for all participants who completed HBOT ($n = 18$) and all who completed placebo ($n = 16$). Change in the direct observation data was calculated by subtracting the average of the baseline observation scores from the average of the final two observation sessions. An ANOVA found no significant differences between groups (Table 4).

2.3. Weekly secondary outcome measures

The ABC, CGI, and RBS were administered weekly. Data were available for these measures for 17/18 participants in the HBOT group and 16/16 participants in the placebo group. There were two significant differences among groups at baseline: the ABC Irritability/Agitation and RBS Self-injurious Behavior subscales were higher in the placebo group. To correct group differences at baseline, all weekly outcome measure scores were adjusted by subtracting the average baseline score.

A repeated-measures ANOVA was conducted for all weekly outcome measures. This model was conducted by using time as a linear covariate, group as a factor, and the time × group interaction, with the adjusted score as the dependent variable. While there was a significant effect for time (weeks in study), none of the analyses found a significant difference among groups (Table 5). That is, both groups improved over time but no difference in improvement was found between the groups.

Table 3
Group comparison on change scores for secondary outcome variables.

	t	df	*p*-value	*d*	HBOT *n*	Placebo *n*
VABS-II communication change	−0.66	32	0.51	0.23	18	16
VABS-II daily living skills change	−0.32	32	0.75	0.11	18	16
VABS-II socialization change	1.10	32	0.28	0.38	18	16
VABS-II adapt. beh. comp. change	0.51	32	0.61	0.18	18	16
VMI-5 change	1.22	30	0.23	0.44	17	15
PPVT-III change	1.17	25	0.25	0.46	14	13
BRIEF-P inhibit change	−0.12	32	0.90	0.4	18	16
BRIEF-P shift change	−0.33	32	0.75	0.11	18	16
BRIEF-P emotional control change	−0.11	32	0.91	0.04	18	16
BRIEF-P BRI change	0.55	22	0.59	0.22	12	12
BRIEF-P initiate change	0.24	22	0.81	0.10	12	12
BRIEF-P working memory change	0.22	32	0.83	0.08	18	16
BRIEF-P plan	−0.14	32	0.89	0.05	18	16
BRIEF-P org. of materials change	−0.18	22	0.86	0.07	12	12
BRIEF-P monitor change	−0.12	22	0.91	0.05	12	12
BRIEF-P MI change	−0.50	32	0.62	0.17	18	16
BRIEF-P GEC change	−0.11	32	0.92	0.04	18	16

Table 4
Group comparison on change scores for behavior observations.

	Mean	S.D.	*F*(1,32)	*p*-value	*f*
Spontaneous toy play			0.38	0.54	0.11
HBOT	7.09	22.57			
Placebo	11.45	17.95			
Hyperactivity			0.016	0.90	0.02
HBOT	2.17	21.83			
Placebo	2.95	13.03			
Appropriate vocalization			0.25	0.62	0.09
HBOT	−1.99	16.36			
Placebo	−4.78	15.96			
Vocal stereotypy			0.74	0.39	0.15
HBOT	6.22	21.76			
Placebo	12.14	17.75			
Physical stereotypy			1.58	0.22	0.21
HBOT	−4.19	18.70			
Placebo	4.67	22.44			
Challenging behaviors			2.59	0.12	0.15
HBOT	−2.71	8.54			
Placebo	1.11	4.32			

Finally, a repeated-measures ANOVA was conducted for the four PSI scores (data available for 18/18 HBOT participants and 16/16 placebo participants). Time and group were used as factors and the PSI total stress score as the dependent variable. Neither time nor group showed a significant effect on PSI total stress scores (Table 5).

2.4. Safety

No participant in this study experienced negative effects attributable to barotrauma (pressure injury to tympanic membranes, sinuses, etc.). One child in the placebo group withdrew as a result of hyponatremia and the acute onset of seizures, which had never been previously observed. The hyponatremia appeared to be secondary to dilution of electrolytes caused by excessive water consumption.

3. Discussion

No significant differences between the HBOT and placebo groups were found on any of the outcome measures. Thus, the results of this study indicate that HBOT delivering 24% oxygen at 1.3 atm did not produce a therapeutic effect for the children who participated in our study. Therefore, HBOT at this dose is not recommended for the treatment of ASD symptoms.

The results of this study corroborate the findings of the only other published study on HBOT which included a control group (Rossignol et al., 2009)—albeit, not the study authors' interpretations of their findings. In both the Rossignol et al.

Table 5
Repeated-measures ANOVA's for secondary outcome measures.

Scale	*F*		*p*-value
ABC irritability/agitation			
Group	*F*(1,31)	0.18	0.675
Week	*F*(1,377)	3.75	0.053
Week* group	*F*(1,377)	0.01	0.903
ABC lethargy/social withdrawal			
Group	*F*(1,31)	0.20	0.660
Week	*F*(1,377)	42.30	<0.001**
Week* group	*F*(1,377)	2.22	0.136
ABC stereotyped behavior			
Group	*F*(1,31)	0.07	0.793
Week	*F*(1,377)	6.24	0.013*
Week* group	*F*(1,377)	0.38	0.537
ABC hyperactivity			
Group	*F*(1,31)	0.00	0.973
Week	*F*(1,377)	11.12	<0.001**
Week* group	*F*(1,377)	0.29	0.589
ABC inappropriate speech			
Group	*F*(1,31)	0.00	0.987
Week	*F*(1,377)	4.14	0.043*
Week* group	*F*(1,377)	1.28	0.259
ABC total score			
Group	*F*(1,31)	0.05	0.831
Week	*F*(1,377)	23.32	<0.001**
Week* group	*F*(1,377)	0.76	0.384
CGI severity			
Group	*F*(1,31)	4.08	0.052
Week	*F*(1,377)	0.68	0.410
Week* group	*F*(1,377)	2.22	0.136
RBS stereotypic behavior			
Group	*F*(1,31)	0.42	0.520
Week	*F*(1,377)	19.26	<0.001**
Week* group	*F*(1,377)	1.33	0.250
RBS self-injurious behavior			
Group	*F*(1,31)	0.00	0.952
Week	*F*(1,377)	1.72	0.191
Week* group	*F*(1,377)	2.46	0.112
RBS compulsive behavior			
Group	*F*(1,31)	2.74	0.108
Week	*F*(1,377)	26.66	<0.001**
Week* group	*F*(1,377)	0.00	0.972
RBS ritualistic behavior			
Group	*F*(1,31)	2.40	0.131
Week	*F*(1,377)	3.55	0.060
Week* group	*F*(1,377)	3.43	0.065
RBS sameness			
Group	*F*(1,31)	0.36	0.553
Week	*F*(1,377)	21.8	<0.001**
Week* group	*F*(1,377)	1.05	0.306
RBS restricted behavior			
Group	*F*(1,31)	0.93	0.341
Week	*F*(1,377)	61.04	<0.001**
Week* group	*F*(1,377)	0.53	0.465
RBS overall			
Group	*F*(1,31)	0.36	0.553
Week	*F*(1,377)	20.69	<0.001**
Week* group	*F*(1,377)	0.39	0.531
PSI total stress			
Group	*F*(1,30)	0.04	0.839
Week	*F*(1,30)	1.62	0.213
Week* group	*F*(1,30)	0.33	0.857

* Significant at the 0.05 level.
** Significant at the 0.001 level.

(2009) study and the current study, both treatment and control groups improved over time, but the difference in improvement between groups appeared insignificant. In addition, the current study employed dependent measures which were far more comprehensive than in previous research on HBOT for ASDs, thereby increasing the probability that a therapeutic effect would have been detected if indeed one had been present.

A limitation of the current study is the restricted sample size. At the onset of this study, no controlled trials of HBOT had been published upon which to conduct an *a priori* power analysis. However, as Rossignol et al. (2007) reported a medium to large effect (Cohen, 1988) on the same primary dependent measure as used in this study, their effect size was used to refine the current study's power estimate. Thus, based upon the revised power analysis, the current sample size would be able to detect large effects that would potentially occur as a result of HBOT. However, the observed effect sizes within the current study were rather small. While it is possible that a larger sample would have yielded greater power to detect a smaller effect, it is questionable whether an effect of that size would be clinically significant.

Another consideration is that both the treatment group and the placebo group received intensive ABA interventions throughout the study. A recent meta-analysis of studies on early intensive behavioral interventions by Reichow and Wolery (2009) found a mean effect size of 0.69 for ABA interventions. Thus, if any potential effects of HBOT were not additive to the effects of ABA then these effects would not have been detected. Nonetheless, the same conclusion is still apparent: that HBOT did not produce a large enough effect to be detected.

With the emergence of greater understanding of the biological factors associated with ASDs comes the potential for alternative medical treatments to compliment existing treatment programs such as the use of ABA for children with ASDs. However, research in these areas is moving much slower than research on the genetics, neurobiology, and nosology of ASD (Matson & LoVullo, 2009). Currently, clinicians are left to speculate and approach the biomedical treatment of their patients through a trial-and-error system in which large costs and unknown risks are weathered in the hope that their patient may respond favorably. Part of this dysfunctional system is the lack of publication of studies with null results. Studies showing a lack of evidence for treatment efficacy are as important as studies demonstrating positive results because they provide important information about treatment approaches with only spurious or anecdotal evidence.

This study found HBOT to have no significant beneficial effect on ASD symptoms. The experimental design of the current study is of a higher rigor than those employed in previous studies which have suggested that HBOT is effective. Further, the dependent measures included were far more comprehensive than those included in previous studies; therefore it is unlikely that an effect was present which was not detected. Based upon the findings of the current study, HBOT delivered at 24% oxygen at 1.3 atmospheric is not recommended for the treatment of ASD symptoms.

Conflict of interest statement

One author, JB is a parent of a child with autism and owns a center which provides HBOT services. All the other authors are employed by the Center for Autism and Related Disorders, a company which provides ABA services.

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