Research in Autism Spectrum Disorders 4 (2010) 268–275

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

Randomized trial of hyperbaric oxygen therapy for children with autism

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ARTICLE INFO

Keywords:
Autism Spectrum Disorders
Autism Treatment
Hyperbaric oxygen therapy
Applied behavior analysis

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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doi:10.1016/j.rasd.2009.09.014

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.