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BRIEF REPORT

Brief Report: Hyperbaric Oxygen Therapy (HBOT) in Children with Autism Spectrum Disorder: A Clinical Trial

Stephen Bent · Kiah Bertoglio · Paul Ashwood · Edward Nemeth · Robert L. Hendren

Abstract We sought to determine whether HBOT leads to parental reported behavioral changes and alterations in cytokines in children with ASD. Ten children completed 80 sessions of HBOT and all improved by 2 points on the clinician-rated CGI-I scale (much improved) as well as several parent-completed measures of behavior. The lack of a control group limits the ability to determine if improvements were related to HBOT. Enrolled children did not exhibit abnormal cytokine levels at baseline and no significant changes in mean cytokine levels were observed. Although this study was limited by the small sample size and by the variable nature of cytokines, we found no evidence that HBOT affects cytokine levels or that cytokine levels were associated with behavioral changes.

Keywords Autism · Clinical trial · Alternative therapy

Clinical Trial Registry: Pilot Study of the Effect of Hyperbaric Oxygen Treatment on Behavioral and Biomarker Measures in Children With Autism (HBOT); NCT00584480; http://www.clinicaltrials.gov/ct2/show/NCT00584480.

S. Bent · R. L. Hendren
Department of Psychiatry, University of California, San Francisco, CA, USA

S. Bent
Osher Center for Integrative Medicine, Department of Medicine, University of California, San Francisco, CA, USA

S. Bent
Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA

S. Bent (✉)
San Francisco VAMC, 111-A1, 4150 Clement St., San Francisco, CA 94121, USA
e-mail: Stephen.Bent@ucsf.edu

Introduction

Hyperbaric oxygen therapy (HBOT) is the term for providing oxygen to a patient at concentrations greater than ambient air (21% oxygen) under increased pressure. HBOT increases the oxygen content of plasma and body tissues (Gill and Bell 2004), and has been shown in animal models to reduce inflammation and improve measures of oxidative stress (Lin et al. 2005; Yasar et al. 2003). HBOT is an effective treatment for decompression sickness (Leach et al. 1998) and is likely effective for the treatment of diabetic foot ulcers (Kranke et al. 2004). Although it is sometimes used for the treatment of other medical conditions that involve acute or chronic hypoxia, there is currently insufficient evidence to determine if HBOT is effective for traumatic brain injury (McDonagh et al. 2004), acute ischemic stroke (McDonagh et al. 2003, idiopathic sudden sensorineural hearing loss (Bennett et al. 2007), and other conditions. A number of case series have shown beneficial effects of HBOT in children with cerebral palsy (CP) (Senechal et al. 2007). The only randomized

K. Bertoglio
University of California, Irvine School of Medicine, Irvine, CA, USA

P. Ashwood
Department of Medical Microbiology and Immunology, University of California, Davis, CA, USA

E. Nemeth
Clinical Hyperbaric Education and Research Institute for Synaptic Healing (C.H.E.R.I.S.H.) Foundation, Sacramento, CA, USA

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controlled trial of HBOT conducted in children with CP found that both the HBOT and the control group improved, but with no significant difference between groups (Collet et al. 2001). This study generated controversy, because the control group used pressurized air, which increases plasma oxygen concentrations and is therefore an active treatment, potentially explaining the similar degrees of improvement in both groups (Senechal et al. 2007).

Since children with autism spectrum disorder (ASD) have been shown to have increased levels of neuroinflammation, altered cytokine levels, and oxidative stress, some researchers have theorized that HBOT might reverse these biochemical abnormalities and therefore improve the symptoms of autism (Rossignol and Rossignol 2006). Several small, uncontrolled case reports and case series reported some improvements in symptom scores in children who were treated with HBOT. To date, there have been two small, randomized, placebo-controlled trials of HBOT in children with autism spectrum disorder (ASD). The first study, published in 2009, randomly assigned 62 children with ASD to 40 1-h treatments of hyperbaric therapy (1.3 atm and 24% oxygen) versus a placebo control of 40 "sham" sessions at 1.03 atm and ambient oxygen levels (21% oxygen). The authors reported that 9/30 (30%) of children in the treatment group were rated as "much improved" or "very much improved" on the Clinical Global Impression-Improvement (CGI-I) score compared to only 2/26 (8%) in the placebo group ($p = 0.0024$) (Rossignol et al. 2009). However, this study was criticized for several methodological problems (Jepson et al. 2010), and it did not show improvements in other outcome measures, including the overall score and the five subscales of the Aberrant Behavior Checklist. A second randomized, placebo-controlled trial (published in 2010) included 34 children with ASD who were randomly assigned to the same level of hyperbaric therapy as the first study (1.3 atm and 24–28% oxygen) and a similar sham control (Granpeesheh et al. 2010). This study found no improvements in a large variety of outcome measures, including the CGI-I (which had improved in the earlier study). The reasons for the discrepant findings of the two studies are unclear. Most recently, a detailed assessment of individual behaviors in 16 children with ASD undergoing hyperbaric therapy (40 sessions of 24% oxygen at 1.3 ATA) found no consistent positive or negative effects in a large number of behaviors (Jepson et al. 2010).

A previous study found that mean CRP levels decreased in 18 children with autism after 40 sessions of HBOT and the largest decreases in CRP were noted in those with initially higher levels of this inflammatory marker. (Rossignol et al. 2007) Due to the open label design of this study, it is not possible to determine if HBOT or regression to the mean was responsible for the observed decrease in CRP, but this study suggests that some plasma measures may correlate with treatment and therefore may have potential as a marker or predictor of response.

Since one of the hypothesized beneficial effects of HBOT in children with ASD is believed to be an alteration in cytokine levels, we sought to determine if a typical treatment course of HBOT would result in changes in plasma cytokines. We further sought to determine if any changes in these cytokines would be correlated with changes in symptoms of ASD, suggesting a potential mechanism of action.

Methods

Participants

The study protocol and all procedures were approved by the Committee on Human Research at the University of California, Davis. The trial was registered prior to enrolling patients at clinicaltrials.gov (Identifier NCT00584480) and took place between October 1, 2007 and April 24, 2009.

Children between the ages of 3 and 8 with a diagnosis of ASD were recruited from the outpatient autism clinic at the MIND Institute (University of California, Davis). The diagnosis of ASD was established using the Autism Diagnostic Observation Scale (ADOS), the Social Communication Questionnaire (SCQ) and by clinical review of the DSM-IV TR criteria by an expert clinician (RLH). Children were required to have a non-verbal IQ of 50 or more, remain on a stable medical regimen, and have a clinician rating of at least moderate severity of autistic symptoms (Clinical Global Impression Severity score of $\geq$4, range 0–7, higher scores indicate more severe symptoms). Children were excluded if they had clinical evidence of seizure disorder, active infection with fever, Fragile X or other known genetic cause of autism, perinatal brain injury (e.g. cerebral palsy), a previous adequate trial (at least 20 session) of HBOT, or inability to clear ears in the HBOT chamber.

Intervention

Children who satisfied all eligibility criteria were enrolled in the study and initiated hyperbaric oxygen therapy (HBOT). Children received 40 days of HBOT (1.5 atmosphere absolute; 100% oxygen) for 1 h, 5 days a week for 8 weeks, followed by a 4 week break, and then another 40 treatments over 8 weeks to complete 80 treatments over 20 weeks. HBOT was provided free of charge to all families by the Clinical Hyperbaric Education and Research Institute for Synaptic Healing (C.H.E.R.I.S.H.) Foundation, Sacramento, CA.

Objectives and Outcomes

All outcome measures were assessed at baseline, after 40 days, and after 80 days of treatment The primary objective of this study was to determine if HBOT resulted in changes in markers of plasma cytokines over the course of the study.

Other outcomes were designed to examine changes in the core features of autism (communication problems, social difficulties, and repetitive/restricted behavior). Communication was assessed with the Peabody Picture Vocabulary Test (measuring receptive vocabulary) and the Expressive Vocabulary Test (measuring expressive vocabulary). Social interaction and behavior were assessed with two parent-completed questionnaires: 1) Aberrant Behavior Checklist (ABC), and 2) Pervasive Developmental Disorder Behavior Inventory (PDDBI). Intelligence was measured with the Stanford Binet-IV. Global changes in the severity of autistic symptoms were evaluated by a clinician with the Clinical Global Impression-Improvement (CGI-I) scale. CGI-I scores were formulated by the clinician based on parent interview of changes in the child's behavior and from direct clinical observation.

Laboratory Methods

Blood was collected in citrate containing tubes from all participants at baseline and immediately after HBOT treatment on the day of treatment. All samples were collected and processed according to the schedule. Plasma was isolated by centrifugation. Cytokine analysis was performed on plasma samples using multiplex assays (Millipore) according to the manufacturer's recommendation and read on a Luminex100™ platform. The cytokines/chemokines analyzed were interleukin (IL)-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, graunolocyte macrophage colony stimulating factor (GM-CSF), G-CSF, eotaxin, interferon gamma (IFNγ), IFNα, tumor necrosis factor alpha (TNFα),TNF-β, monocyte chemotractic protein (MCP)-1, transforming growth factor beta 2 (TGFβ-2), macrophage inflammatory protein (MIP)-1α, MIP-1β, 10 kDa interferon-gamma-induced protein (IP-10) and brain derived neurotrophic factor (BDNF). Activated TGFβ1 was analysed using a separate ELISA (R and D systems) and was performed according to the manufacturer's instructions. Intra and inter- plate/assay variations of cytokine levels, using representative samples run on all plates, were less than 5%.

Statistical Methods

We compared baseline scores for each study variable (plasma cytokines and scores from the parent-completed measures) with values at the midpoint (40 days) and closeout (80 days) of the study. Changes between two timepoints (baseline to 40 days and baseline to 80 days) were compared with the student's t-test, and changes over the course of the study were analyzed using an analysis of variance (ANOVA). Because this was designed as an exploratory analysis, we did not adjust p-values for multiple testing. All reported p-values are two-sided.

Results

Children who met all inclusion and no exclusion criteria were selected from the MIND Institute research subject tracking database and the first 10 subjects whose families expressed an interest in participating were enrolled in the study protocol. Table 1 shows the characteristics of the enrolled children, who had a mean age of 5.3 years (range 3.3–7.5 years, SD = 1.8) and had a mean Global Clinical Impression Severity score of 5.0 (range 0–7, higher is worse), indicating that children were "markedly ill." No subjects dropped out of the study.

The overall improvement in symptoms related to autism was assessed with the Clinical Global Impression-Improvement (CGI-I) scale (where scores of 0 = no improvement, 1 = minimally improved, 2 = much improved, and 3 = very much improved). At 40 days, 5 of the 10 children were rated as 1 (minimally improved) and the other five were rated as 2 (much improved). At 80 days, all 10 children were rated as 2 (much improved; $p = 0.004$ for change from baseline to 80 days). The most common improvements reported by parents were in the areas of imitation (6), eye contact (4), language (4), less frequent or less severe tantrums (3), gastrointestinal problems (2), and eczema (1).

Changes in other measures of symptoms of autism over the course of the study are shown in Table 2.

The Aberrant Behavior Checklist (ABC) showed statistically significant improvements in 3 of the 5 subscales

Table 1 Baseline characteristics of enrolled children

Characteristic	Mean (SD) or proportion (percent)
Age (years)	5.3 (1.8)
Clinical global impression—improvement	5.00 (0.67)
Stanford Binet—IQ scores	
Verbal	4.80 (5.41)
Non-verbal	3.00 (2.45)
Associated conditions	
Food allergy	4/10 (40%)
Gastrointestinal symptoms	4/10 (40%)
Frequent infections	6/10 (60%)
Regression	3/10 (30%)

Table 2 Changes in clinical outcome measures

Outcome	Baseline mean (SD)	40 Day mean (SD)	80 Day mean (SD)	Change† (80 day-baseline)	95% CI for change	*p*-value
Measure:						
ABC						
Irritability	13.9 (2.4)	10.0 (2.4)	9.7 (2.4)	4.2 (1.5)	1.0 to 7.4	0.01
Lethargy	13.7 (1.8)	8.6 (1.8)	6.6 (1.9)	7.1 (1.4)	4.1 to 10.1	0.0001
Stereotypy	7.4 (1.8)	6.4 (1.8)	5.7 (1.8)	1.7 (1.0)	−0.4 to 3.7	0.10
Hyperactivity	21.9 (3.1)	15.7 (3.1)	16.2 (3.2)	5.7 (2.3)	0.9 to 10.6	0.02
Inappropriate Speech	3.7 (1.1)	2.6 (1.1)	3.0 (1.1)	0.7 (0.8)	−1.0 to 2.4	0.42
Total	60.6 (7.7)	43.3 (7.7)	41.1 (7.9)	19.5 (5.3)	8.4 to 30.6	0.002
PDD-BI						
Sensory	56.6 (3.3)	51.5 (3.3)	46.4 (3.4)	10.2 (2.7)	4.5 to 15.9	0.001
Ritual	51.6 (4.0)	49.8 (4.0)	47.4 (4.1)	4.2 (2.3)	−0.7 to 9.2	0.09
Social/Pragmatic	52.1 (3.2)	49.5 (3.2)	49.3 (3.3)	2.8 (2.2)	−1.8 to 7.5	0.22
Semantic	52.6 (3.8)	53.3 (3.8)	49.9 (3.8)	2.7 (2.7)	−3.1 to 8.5	0.35
Arousal regulation	51.8 (3.9)	55.3 (3.9)	50.5 (4.1)	1.3 (4.8)	−8.9 to 11.5	0.80
Specific fears	54.5 (3.0)	53.1 (3.0)	47.2 (3.1)	7.3 (2.4)	2.4 to 12.3	0.006
Aggressiveness	57.0 (4.7)	51.6 (4.7)	46.5 (4.8)	10.5 (2.4)	5.4 to 15.6	0.0005
Social approach	42.4 (3.1)	43.7 (3.1)	46.3 (3.1)	3.9 (2.2)	−0.6 to 8.5	0.09
Expressive lang	46.2 (3.1)	46.6 (3.1)	47.5 (3.2)	1.3 (1.8)	−2.5 to 5.1	0.48
Learning, memory	42.3 (3.6)	44.4 (3.6)	46.2 (3.7)	3.9 (2.0)	−0.3 to 8.1	0.07
PIA-CV	308 (9)	320 (9)	348 (9)	39 (10)	18 to 60	0.001
PPVT	42.4 (8.1)	47.1 (8.1)	51.9 (8.2)	9.5 (4.3)	0.4 to 18.6	0.041
SB-V	4.8 (1.7)	5.3 (1.7)	4.5 (1.7)	−0.3 (1.0)	−2.4 to 1.9	0.79
SB-NV	3.0 (0.9)	3.8 (0.9)	4.2 (0.9)	1.2 (0.8)	−0.4 to 2.8	0.14

ABC aberrant behavior checklist, *PDD-BI* pervasive developmental disorder behavior inventory, *PIA-CV* parent interview for autism, clinical version, *PPVT* peabody picture vocabulary test, *SB-V* Stanford Binet verbal intelligence, *SB-NV* Stanford Binet non-verbal intelligence

† All changes were coded so that positive values indicate improvement, even when the scores decreased from baseline (for the social approach, expressive language, and learning/memory subscales of the PDD-BI, higher scores indicate improvement; for all other subscales, higher scores indicate more severe symptoms)

(irritability, lethargy, and hyperactivity) as well as the total score. Similarly, the Pervasive Developmental Disorder Behavior Inventory (PDDBI) showed statistically significant improvements over the course of the study in three of the ten subscales, and all other subscales showed non-significant changes in the direction of improvement. The Parent Interview for Autism, Clinical Version also improved over the course of the study ($p = 0.001$). In terms of language and intelligence tests, the enrolled subjects showed an improvement in receptive vocabulary (as measured by the Peabody Picture Vocabulary Test), but no changes in non-verbal or verbal intelligence testing on the Stanford-Binet instrument.

Changes in plasma cytokines over the course of the study are shown in Table 3.

There were no statistically significant changes in any of the 29 measured cytokines over the course of the study. In a post-hoc analysis, we also examined whether the mean number of cytokines with detectable values changed during the course of the study, and there was no statistically significant change (25.4 detectable cytokines at baseline versus 26.0 at termination, $p = 0.58$).

Fourteen non-serious adverse events were reported during the course of the study. Three children reported ear discomfort during the course of the study; two other children reported ear infections. Other adverse events experienced during the study included: increased hyperactivity (1), increased vocal sensitivity (1), increased sensory needs (1), insomnia (1), dehydration (1), fatigue (1), irritability (1), increased mouthing of objects (1), and seizure (1). The ear pain, increased fatigue, dehydration, and increased mouthing of objects were judged to be likely related to the HBOT treatment.

Discussion

Parent reported measures of symptoms improved markedly in this group of children who were treated with HBOT as reflected by improvements in the ABC (which assesses

Table 3 Changes in cytokines during the study

Cytokine	Baseline mean	SD	Day 40 mean	SD	Day 80 mean	SD	*p* value
TGF_b_1	8.64	0.25	9.15	0.26	8.90	0.28	0.49
TGF_b_2	8.68	0.25	9.23	0.27	8.98	0.28	0.44
BDNF	5.97	0.25	6.48	0.26	6.14	0.27	0.63
IL_1a	5.05	0.19	5.01	0.20	5.32	0.21	0.26
IL_1b	0.31	0.29	−0.06	0.32	−0.02	0.32	0.41
IL_2	0.73	0.35	0.10	0.36	0.42	0.38	0.46
IL_3	1.73	0.08	1.59	0.09	1.59	0.09	0.28
IL_4	0.24	0.53	−0.29	0.54	0.22	0.56	0.98
IL_5	−0.06	0.42	−0.51	0.42	−0.02	0.44	0.92
IL_6	0.81	0.50	0.34	0.51	1.23	0.52	0.42
IL_7	0.84	0.50	0.77	0.51	0.69	0.54	0.80
IL_8	1.37	0.27	1.51	0.28	1.67	0.29	0.42
IL_10	1.92	0.23	1.80	0.23	1.92	0.24	0.99
IL_12_p40	4.50	0.40	4.81	0.40	4.67	0.41	0.61
IL_12_p70	1.62	0.35	1.15	0.36	1.67	0.38	0.89
IL_13	0.09	0.35	0.00	0.36	0.14	0.37	0.90
IL_15	1.11	0.13	0.93	0.13	0.97	0.14	0.33
IL_17	1.09	0.42	0.98	0.43	1.57	0.44	0.26
IP_10	5.54	0.21	5.50	0.22	5.87	0.23	0.22
MCP_1	5.78	0.06	5.80	0.06	5.83	0.07	0.55
MIP_1a	3.44	0.36	3.60	0.36	3.70	0.37	0.34
MIP_1b	3.32	0.25	3.22	0.25	3.31	0.26	0.97
TNF_a	1.75	0.09	1.79	0.09	1.79	0.09	0.74
TNF_b	1.47	0.31	0.84	0.34	0.85	0.34	0.17
INF_g	1.85	0.36	1.69	0.37	1.96	0.39	0.80
INF_a2	5.05	0.19	5.01	0.20	5.32	0.21	0.25
GM_CSF	3.70	0.30	3.28	0.30	3.67	0.32	0.94
G_CSF	3.89	0.22	3.98	0.23	3.91	0.24	0.93
Eotaxin	4.52	0.14	4.56	0.14	4.53	0.15	0.96

All units are expressed in picograms/milliliter. *TGF* tumor growth factor, *BDNF* brain-derived neurotrophic factor, *IL* interleukin, *IP-10* 10 kDa interferon-gamma-induced protein, *MCP-1* monocyte chemotactic protein-1, *MIP* macrophage inflammatory protein, *TNF* tumor necrosis factor, *INF* interferon, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *G-CSF* granulocyte colony-stimulating factor. Cytokine concentrations can have negative values because they are log transformed

problem behaviors) and the PDD-BI (which assesses a broad range of symptoms of autism). This is consistent with findings from other open-label studies of HBOT. Beneficial effects in open-label studies of autism may be due to a placebo effect, natural changes in the symptoms in individual children, reporting bias, or a true beneficial effect of the intervention. The relatively long treatment period in this study (20 weeks) may have provided an opportunity for children to improve from other concurrent interventions. The open-label design of the current study does not provide strong evidence either supporting or refuting the efficacy of HBOT. A recent very detailed study of 16 children with ASD who underwent video-taped ratings by clinicians of play sessions before, during, and after HBOT found no improvements in a large number of behaviors (Jepson et al. 2010). Since almost all of the symptom measures in the current study were parent-reported instruments (ABC and PDD-BI) or were clinician ratings based in part on interviews with parents (CGI-I), it is possible that the placebo effect or parental reporting bias may have led to the observed improvement in these outcome measures. Given these caveats, it is possible that HBOT accounted for the clinical improvements noted in the study, especially since significant improvements over a 20 week period in children with autism are not necessarily expected.

We found no evidence that HBOT changed measures of plasma cytokines over 80 treatment sessions. This may indicate that HBOT does not alter cytokine levels in children with ASD, but could also be due to the fact that enrolled patients did not have abnormal baseline levels of plasma cytokines or because cytokines are highly variable

(and this variability limited the power to detect changes). Although it is expected that cytokine levels in the plasma of typically developing individuals would be low, cytokine values may vary depending on the specific technology used to assess their levels. There are currently no clinically validated reference ranges for measures of cytokine levels in the plasma in typically developing individuals. However, since parents reported clinical improvements—if these improvements were mediated by changes in the cytokines assessed—we would have expected to see changes in at least some of these cytokine levels. We did not select children based on their initial cytokine levels for two main reasons: first, we sought to model typical clinical use of HBOT for children with autism, where the treatment is most commonly administered to children without screening for elevated baseline cytokine levels; second, the selection of children with high initial cytokine levels could have led to regression to the mean, which could produce an apparent (but untrue) appearance of a decrease in cytokine levels with the use of HBOT.

The primary limitation of this study is the small sample size, which may have provided limited power to detect changes in plasma cytokines. Also, the lack of control group prevented an examination of whether changes in clinical measures of disease severity were due to HBOT or other factors. Another limitation of the current study is that we did not measure cytokines in the brain, CSF or mucosal components, each of which has shown elevated cytokine levels in prior studies of children with autism (Ashwood and Van de Water 2004; Vargas et al. 2005).

In conclusion, we found no evidence that HBOT affects plasma cytokine levels in a group of children with ASD who were believed to have beneficial effects based on parent assessments. Enrolled children did not have baseline elevations in cytokines, and cytokine levels are highly variable, both of which limit the ability of this study to identify changes in these markers. Future studies of HBOT should consider including other possible measures of a mechanism of action in addition to cytokines. In addition, future HBOT studies might consider enrolling subjects with elevated cytokines or other baseline measures and using a randomized controlled trial design to improve determinations of efficacy and mechanism of action.

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